A Report to the Congress
From the Secretary
Department of Health, Education, and Welfare

Marihuana and Health

January 31, 1971

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INTRODUCTION

This report has been prepared in accordance with the "Marihuana and Health Reporting Act" (Title V of P.L. 91-296) which requires submission by the Secretary of Health, Education, and Welfare of annual reports to the Congress on the health consequences of marihuana usage. Unlike the preliminary report of September 1970, which more briefly outlined the nature of the research questions currently being posed and the Federal program designed to elicit some of the answers, the present report is designed to summarize the current status of our knowledge of the health consequences of marihuana use. "Health consequences" for the purposes of this document include not only the effects of the drug on the individual's physical and psychological health but also the effects of cannabis use on the society.

As was indicated in the report of September 1970, the health picture with respect to marihuana must at present be regarded as fragmentary and clearly incomplete. Many of the most important questions regarding the implications of long-term, chronic use will require significant periods of time to answer. Extrapolation from data based on cultures which are in many respects significantly different from our own is inevitably hazardous. The picture is further complicated by the degree to which drugs as actually used in a given society differ from pure laboratory chemicals. Thus, we are forced to rely on lines of evidence each in

itself admittedly incomplete but which taken together will ultimately converge toward reliable and valid conclusions regarding marihuana and health.

Sources of Information

A wide variety of sources of information have been used in preparing this report. Careful consideration has been given to the convergence of evidence to support a particular finding; or, in the absence of this, the confidence placed in the statement has been accordingly reduced. It should be noted that the information upon which this report is based includes both published and unpublished reports from grantees of the National Institute of Mental Health and investigators who were supplied with quantities of marihuana (in various forms and potencies), and who, in turn, have shared the results of their research with us.

Published results of surveys, studies and experiments from many scientific sources have been carefully reviewed. Selected articles from journals, newspaper articles of high quality, government reports concerning marihuana use in other countries, ranging from the Indian Hemp Commission of the last century to the recent Le Dain Commission of Canada, have also been used and provide a picture of marihuana use in other regions of the new and old world. Reports of consultants, as well as the proceedings of various symposia and conferences, have been studied.

It is important to recognize that any one source of information is inevitably subject to limitations inherent in the research design. Thus,

no single study can be regarded as definitive. Conclusions that are drawn or persistent uncertainties are a function of the information available at any given point in time. Final judgments, given our present limitation of knowledge, are not possible at this time. A balanced, objective analysis of the health implications of marihuana must consist of a series of successive approximations as our information becomes increasingly complete.

In order to be of value to the more scientifically sophisticated reader, some portions of this report are inevitably technical. Wherever these technical portions have lent themselves readily to translation into more widely understood language, this has been done. In some portions, notably those on the chemical characteristics of natural and synthetic materials, in which such a translation is neither readily possible nor essential to a general understanding of the report, no such attempt has been made. In this way it is hoped that the report will meet both the needs of the general reader and to some extent those of the technically sophisticated as well.

SUMMARY

In this, the first detailed report to the Congress on Marihuana and Health, an attempt has been made to accurately describe the present state of our scientific knowledge concerning this issue. Not unlike a rather elaborate jigsaw puzzle, however, there are many research "pieces" whose relation to one another is not obvious. Moreover, many of the most important pieces that are required are not yet available. Some of the technical data that have been accumulated remain obscure for the present, particularly in providing a picture comprehensible to the layman. The ultimate meaning of past, present and future research will only become clearer as the various parts can be related to an emerging whole.

The purpose of this summary is to try to translate the present disparate elements into as reasonable an answer as can currently be framed to the question: What are the health implications of marihuana use for the American people? It does not attempt to evaluate broader legal, economic or social issues including the consequences of law enforcement for personal marihuana use even though they are important and must be considered in a complete discussion of the overall problem.

As we examine the drug in its various natural and synthetic forms, however, it becomes evident that the deceptively simple question posed is highly complex and marihuana is not a single, simple substance of uniform type. It consists of varying mixtures of different parts of the plant, Cannabis sativa, with psychoactive properties ranging from virtually nonexistent to decidedly hallucinogenic in its stronger forms and at high doses. Unfortunately, much of the discussion in lay and

sometimes scientific forums ignores this very basic and important fact. Most of our American experience has been limited to the widespread relatively infrequent use of a rather weak form of marihuana. Early research dealing with the drug is inevitably faulted by the fact that it is difficult to be certain just what potency material was involved and at what dose level. Although the principal active ingredient in the plant is thought to be Delta-9-tetrahydrocannabinol, much remains to be learned about the chemistry of marihuana and related substances.

Even the form in which the drug is consumed may make a difference in the consequences of use. It is quite possible, for example, that when smoked the material taken into the body differs significantly from orally consumed drug. The route of absorption, whether through the lungs or the digestive tract, may also make a significant difference in the consequences of use.

Virtually all of the American data indicate that use of marihuana has rapidly increased over the past several years. While the number of those who have tried the substance at some point in their lives remains a minority of the population it is continuing to increase rapidly. In some high school or college settings it is virtually certain that a majority have at least tried marihuana. By the end of 1970 about one college student in seven was using it on a weekly or more frequent basis. High school use has generally lagged behind that of colleges and universities, although in areas of high use as many as a third to a half have experimented with it.

While comparable data are not available for non-school attending youth there is reason to believe that levels of use are at least comparable and for school drop outs are probably higher. In some west coast high schools which have had relatively high levels of use there is evidence that the increase in use may be decelerating and even declining. The likelihood of continuing,persistent use over an extended period of time by large numbers is not known at the present time.

Middle class users have tended to be individuals from higher income families attending larger, non-religiously affiliated urban universities rather than small, denominational colleges. However, as the number of users increases they become less clearly distinguishable from the more general youthful population. As use becomes more widespread there is reason to believe still younger as well as older populations are becoming involved.

Rather than being restricted to our own affluent society, marihuana use as a recent source of concern is a problem in many countries of the world. In at least three other English-speaking countries this concern has led to the appointment of commissions to examine the problem and to issue reports (Canada, England and New Zealand). While in 1956 the United Nations Commission of Narcotic Drugs estimated that over two hundred million people made regular use of cannabis, it is very likely the number is now substantially larger.

The bulk of this report makes clear that while there is much yet to be learned about cannabis, there is a substantial body of information at present available. Much of it is, however, of only limited immediate relevance to the question of the long-term health implications of use.

Subjective Effects

A range of studies have been conducted of the drug's acute effects. As is true of other drugs, generally the effects are closely related to the amount that is consumed. There is general agreement that at the usual levels of social usage the typical subjective effects are: Alteration of time and space perception, sense of euphoria, relaxation, well being and disinhibition, dulling of attention, fragmentation of thought, impaired immediate memory, an altered sense of identity, exaggerated laughter and increased suggestibility. Other less common effects are dizziness, a feeling of lightness, nausea, and hunger. As doses higher than the typical social dose are consumed more pronounced thought distortions may occur including a disrupted sense of one's own body, a sense of personal unreality-of being unreal, visual distortions, sometimes hallucinations and paranoid thinking. The more marked distortions of reality or psychotic-like symptoms become increasingly common if the dosage used becomes extremely high. Most users smoke to the point of "high" which they find pleasurable and at which they are able to control the effect. It is, however, difficult to predict individual reactions. Rarely, individuals may become quite anxious or panicky on even low doses. When eaten, effects are less predictable and more difficult for the user to control.

In addition to the amount of the drug that is consumed, the set and setting of use are important factors in determining marihuana's subjective effects. Set refers to the attitudes, mood, expectations and beliefs which the individual brings to the drug using experience. Setting represents the external circumstances surrounding the experience. Thus a relatively emotionally neutral laboratory setting may evoke very different responses at a given dose

level than might a more typical setting of social usage surrounded by other drug users. A situation in which the individual is depressed or apprehensive about the drug's effects differs markedly from one in which the user is more sanguine and looks forward to the drug experience with eager anticipation. The degree of personality integration, psychological rigidity and the presence or absence of psychopathology are all important contributors to one's subjective reactions to marihuana or other psychoactive drugs.

All of these psychological aspects also play a role in what is often referred to as the "placebo effect." The placebo effect is the response to the substance based not on its pharmacological activity but on the totality of expectations brought about by the set and setting of use. It is not uncommon for individuals consuming a psychoactively inert material to experience subjective effects which they erroneously attribute to an active drug. This same placebo effect may complicate results in a laboratory setting, in which the placebo is so compounded as to resemble the active material in all respects except for the presence of the psychoactive constituents. Particularly at low doses, it may be difficult to be certain to what extent an effect is brought about by the drug itself or placebo effects.

Physiological Effects of Acute Marihuana Use

Physiological changes accompanying marihuana use at typical levels of American social usage are relatively few. One of the most consistent is an increase in pulse rate. Another is a reddening of the eyes at the time of use. Dryness of the mouth and throat are uniformly reported. Although enlargement of the pupils was an earlier impression, more careful study has indicated that this does not occur. Blood pressure effects have been

inconsistent. Some have reported slightly lowered blood pressure while others have reported small increases. Basal metabolic rate, temperature, respiration rate, lung vital capacity and a wide range of other physiological measures are generally unchanged over a relatively wide dosage range of both marihuana and the synthetic form of the principal psychoactive agent, delta-9-THC.

Neurological examinations consistently reveal no major abnormalities during marihuana intoxication. However, some investigators have found a small decrease in leg, hand and finger strength at higher dosages. Some decrease in hand steadiness and the ability to maintain balance occurs as dosages increase. Although users often report enhanced sensory awareness in the drugged state, objectively measurable improvements in visual acuity, brightness discrimination, touch discrimination, auditory acuity, olfactory threshold or taste discrimination have not been found. Some small changes in electroencephalograph (EEG) findings have been detected but the significance of these results is in doubt.

From the standpoint of lethality, cannabis products must be counted among the safer of the drugs in widespread use. Death directly attributable to the drug's effects is extremely rare even at very high doses.

Acute Psychotic Episodes

Acute psychotic episodes precipitated by marihuana intoxication have been reported by a number of investigators. These appear to occur infrequently, usually at high dosages, but may occur, even at levels of social usage, in particularly susceptible individuals. Heightened susceptibility

appears to be more likely in those who have previously had a marginal psychological adjustment especially in the presence of excessive stress.

Intellectual and Motor Performance

Changes in time sense have definitely been shown to take place during marihuana intoxication. There is a tendency to overestimate the passage of time particularly while engaged in some activity.

A wide range of tests of intellectual functioning and of psychomotor performance (the ability to precisely coordinate sensory perception and muscular performance) have been carried out under conditions of intoxication. As might be expected, the degree of impairment is dose related. It also varies during the period of intoxication.

Generally, the more complex and demanding the task to be performed the greater is the degree of impairment. Simple and very familiar tasks such as reciting the alphabet or repeating a brief series of numbers are least likely to be affected at relatively low dose levels. As the task becomes more complicated, however, decrements in performance do become apparent. Inexperienced users tend to show greater decrements than do experienced marihuana users.

Because of the importance the automobile assumes in our society, the effect of marihuana on driving performance is of fundamental interest. One widely reported finding using a driver simulator was that the performance of marihuana using drivers was equal on the average to that of a non-intoxicated control group. It is, however, important to note that this was based on a single study of intoxicated drivers under test conditions that might be

expected to be highly motivating. In addition, half the drivers in the experimental group did more poorly than did the control group. This suggests that the ability to compensate for the effects of marihuana - to suppress the "high" - may differ markedly from individual to individual. The relevance of this work to more typical driving conditions is not known.

It is noteworthy that in another series of studies not directly concerned with driving, marihuana intoxicated subjects consistently answered, "No!" when asked, "Do you think you could drive a car now?". Preliminary results of a study of attention skills believed to be among the best predictors of actual driving performance have shown performance decrements under marihuana use similar to those found when drivers have consumed moderate amounts of alcohol. Additional much needed research on driver performance and other complex motor tasks is currently in progress.

Marihuana users consistently report that their short-term and immediate memory while under the influence of the drug is interfered with. Systematic research evaluation generally confirms this. More complex functions such as learning a number code, using such a code for encoding a series of numbers, understanding a written paragraph or spoken speech are all interfered with even at the moderate levels of typical American social usage. This is believed to reflect difficulty in retaining, coordinating and indexing over time those memories, perceptions and expectations demanded by the task being performed.

Marihuana and Birth Defects

A basic concern with any drug substance coming into wide use is the possibility that it may affect fetal mortality or fetal development (i.e. may be teratogenic) in such a way as to bring about abnormal offspring of pregnant users. It may also conceivably affect unborn generations by causing chromosomal changes (i.e. may be mutagenic) that persistently alter the genetic heritage. Thus far there is little evidence that marihuana or related materials do this. While preliminary studies of the effects of injecting relatively large quantities of cannabis or related substances have found some indication of fetal abnormalities in rats, other researchers have been unable to duplicate such findings. There is no evidence to suggest that marihuana use in humans affects fetal development. Despite the present absence of such evidence, it is obviously unwise for anyone to use any drug of unknown teratogenic or mutagenic properties during the child bearing years. Use during pregnancy is particularly unwise.

Effects of Long-Term Chronic Use

While a good deal is known about the acute effect of cannabis use and the laboratory findings to date generally correlate well with user reports, much less is known about the implications of long term chronic use. In few experimental studies has marihuana been administered to humans for extended periods. These periods have been limited at most to a few weeks. In addition, earlier studies of both acute and chronic use have provided no indication of the exact amounts of psychoactive material involved and so it is difficult to compare those findings with those of contemporary research. Over a period of just under six weeks, one investigator found only small physiological changes when individuals were permitted to consume the drug freely in whatever quantity they chose. A daily mean of 17 cigarettes each was consumed by this group of prisoners.There was some mild confusion under those conditions of continued intoxication with slight impairment of performance on general intelligence testing during the period. While mild changes in electroencephalograph findings were found, these returned to normal five days after discontinuing the drug. There was no evidence of withdrawal effects (i.e. physical symptoms precipitated by discontinuing the drug) after this duration of use.

It should be emphasized that early attempts at evaluating the effects of long-term use of cannabis suffer from multiple scientific defects. Whether they tend to indict or to absolve cannabis from causing chronic physical or psychosocial consequences, it is difficult to be certain of the validity of their observations. The Indian Hemp Commission Report, for example, although a careful, systematic study for its day (the 1890's), can hardly be regarded as meeting modern epidemiological research standards. Subsequent

studies such as those of the group appointed by the then Mayor LaGuardia in New York City can also be easily faulted for their scientific deficiencies. While psychoses presumably resulting from heavy cannabis use have been reported, these studies do not generally meet modern scientific standards.

The fact that there are many worldwide reports of heavy, chronic cannabis use resulting in loss of conventional motivation and in social indifference is of particular interest in that there are now some reports of somewhat similar findings among American heavy users of marihuana. Unfortunately, American use patterns are frequently contaminated by the use of other drug substances, making interpretation difficult. It is not certain to what degree this "amotivational syndrome" is the result of marihuana use per se or of a tendency for those who lack conventional motivation to find drugs unusually attractive. If one confines his use of the term to a description of the present American scene one must conclude that present evidence does not permit the establishment of a causal relationship between marihuana use and the amotivational syndrome. There is, however, increasing evidence that frequent, heavy marihuana use is correlated with a loss of interest in conventional goals and the development of a kind of lethargy. Research in humans is being conducted in an attempt to determine to what extent this observed correlation is due to alteration in brain functioning.

The issue of long-term mental deficit is an exceedingly complex one in which the lack of sufficiently sophisticated methodology may be crucial. The problem of determining harmful effects of chronic use and especially of psychological harm as a result of using a drug substance whose effects are not dramatic is very difficult. Unless the type of deficit is especially distinctive, it is likely that the same symptoms will be exhibited by many non-drug users. Furthermore, unless the harm done to the user is so gross as to

be noticeable in a high percentage of users, it may readily be attributed to other factors such as poverty or poor nutrition. Tobacco furnishes an apt example of the difficulties encountered in demonstrating even physical hazards of use. It was only after many years of use by a substantial segment of the population that the role of smoking in the development of various types of diseases was recognized. It should be noted that concern has been expressed that marihuana when smoked in large quantities might be expected to have similar carcinogenic effects to those associated with cigarette smoking. There is, however, no present evidence to suggest that marihuana is cancer-producing.

Marihuana and the Use of Other Drugs

It is generally conceded that marihuana use does not necessarily lead directly to the use of other drugs. On a worldwide basis there is little evidence of a progression from the use of marihuana to that of opiates or hallucinogens. However, those who find use of marihuana highly attractive, may also be attracted to the use of other drug substances which may be popular among their peers. These may include stronger hallucinogens, amphetamines and the opiates. While it is true that a high percentage of heroin addicts have used marihuana as well, most marihuana users both here and abroad do not appear to be attracted to the use of heroin.

Future Research Directions

It is evident that much remains to be learned about marihuana, hashish and related materials. Little is as yet known about the implications of chronic use particularly at lower dose levels and less frequent intervals. Although much can be learned from animal research, in the final analysis

the most crucial information with respect to long-term human use can only be obtained by careful observations of chronically using groups here and abroad. Such research is currently being carried out.

It is important that we learn more about the possible interactions between marihuana use and that of a wide range of other drugs. This includes not only such drug substances as caffeine, tobacco and alcohol, but also other drugs of abuse and a wide spectrum of therapeutically employed drugs. As use of marihuana comes to include a wider spectrum of the population it is important that we learn its effects on those whose physiological functioning is to some degree impaired or who suffer from physical or psychological disabilities. Such effects must be studied over a wide dosage range and in various use patterns.

From a psychosocial point of view it is essential that we come to better understand the different patterns of drug use, their implications for social functioning and those factors which contribute to such use. These include parental attitudes, child rearing practices and peer pressures as well as those aspects of subcultural and cultural practices that may affect use. Finally, it is imperative that we determine what are more effective prevention and education techniques that serve to avert drug abuse of all types including that of marihuana.

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THE NATURAL AND SYNTHETIC MATERIAL

Plant Material

Chemistry of Marihuana

Synthetic Material

Extract

THE NATURAL AND SYNTHETIC MATERIAL

As illicitly sold, what is called marihuana in the United States may vary from carefully prepared plant material of high potency to psychoactively inert materials masquerading as marihuana. Such adulterants as catnip, oregano and tea are sometimes part of the mixture in order to increase the profit of the seller. The less sophisticated the buyer the more likely he is to obtain inferior or substitute material. Because of the important role that psychological factors play in the effects of psychoactive drugs, users may obtain a subjective high even though the substance used is actually inert or very nearly so. Thus it is important to recognize at the outset that marihuana and related materials encompass an unusually wide range of substances with highly variable psychoactive potential. At least part of the current emotionally charged debate over this group of substances is the result of a failure to adequately specify the material both by dosage and level of psychoactivity, usually expressed in terms of the percentage of Delta 9-THC (the presumed principal psychoactive ingredient) contained in a given sample. Most early research suffers from the serious deficiency that it is impossible to be certain what dosages and strength of material were involved in the work done.

Plant Material

What is commonly called marihuana in North America consists of a mixture of crushed leaves, flowers and often twigs of the Indian hemp plant. This herbaceous annual readily grows in temperate and tropical climates in many parts of the world including the United States, and can reach 15-20 feet in height. (4) Although there are many varieties,

it is now generally agreed that they all belong to a single species, Cannabis Sativa, which exhibit variations because of genetic plasticity and different enviornmental conditions. (13) Cannabis is dioecious, i.e., it has separate male (staminate) and female (pistillate) plants. The male plants are taller and short lived, usually dying after pollen is shed. The female plants are bushier, pollinate and survive until killed by frost or their seeds are fully mature. Both types are indistinguishable until the flower buds are well developed. Male flower clusters have usually little foliage and are borne in leaf axils as loosely arranged clusters, while the female clusters are more densely packed. Complete descriptions of the morphology and botanical characteristics of Cannabis Sativa have been published. (12,3,14) The flowering tops of the female plants secrete a clear, varnish-like resin called "hashish" in the West and "charas" in India. They contain the most concentrated psychoactive material. Other Cannabis preparations containing mixtures of leaves and resin of various potency include bhang and ganga (India), maconha (Brazil), kif and dagga (Africa). The two Cannabis preparations most commonly used in the United States are native or imported marihuana and imported hashish.

It is well known that marihuana from different areas differs in potency and that drug users prefer certain sources of marihuana for their higher potency such as "Panama Red, Acapulco Gold, Texas Black and Vietnam Red." Using analytical methods such as gas chromatography, it is now possible to relate differences in potency to differences in the chemical composition of marihuana from these various sources. It has been shown that the amount and ratio of the components in marihuana are a function of innate botanical (genetic) factors and conditions of growth, as well as

of the mode of preparation of the crude drug and the condition of its storage, such as exposure to light, heat and elapsed time since harvesting. Cannabis has spread throughout the United States along the major rivers and there is a correlation between Cannabis distribution and alluvial stream deposits in areas of the plain states where intermittent flooding occurs. (6)

Contrary to prior beliefs, recent investigations have shown that both the male and female plants contain psychoactive material. (16) The various parts of the plants differ, however, in the percentage of active principles they contain, with the higher parts (flowering tops, bracts and leaves) having the highest percentage of tetrahydrocannabinols, and the lowest parts (stems, seeds and roots) the smallest. The mode of preparation of marihuana becomes, therefore, quite important. A carefully manicured sample containing mostly the upper parts of the plant typically is more potent than one containing a higher proportion of stems and leaves. The resin itself contains five to ten times more psychoactive ingredient than the leaves.

It is now believed that there are two genotypes of marihuana--the drug type with a high percentage of tetrahydrocannabinol (1-5%) and the fiber type with a high percentage of cannabidiol. (17) Analysis of wild Midwestern marihuana (Iowa, Indiana) has shown that the plants contained predominantly cannabidiol (CBD) with only small amounts of THC. Cyclic peaking of cannabidiol occurs during the growing season, with the THC content inversely proportional to the CBD content. THC content is usually low on the same day that the cannabidiol is high and vice versa. (11) This suggests that cannabidiol may be a precursor of THC in the plant as proposed by Mechoulam. (8)

Chemistry of Marihuana

The variation in potency between different sources which has hampered research on marihuana, could not be explained until the mid 1960's when the structure of the active components of marihuana was finally elucidated. (5) Up to that time, the situation for marihuana contrasted sharply with that for other drugs of abuse, such as morphine and cocaine. These drugs, also originating from natural sources and used for illicit purposes, were well known chemical entities and research on their effects could be easily duplicated.

Prior to 1964, the biologists and clinicians studying marihuana believed that the chemistry of marihuana components had been elucidated by early studies of Adams and Todd in 1940. Numerous "cannabinoids" were known to be present in the resin and the plant but the structure of only one, cannabinol, had been fully elucidated. (1, 15)

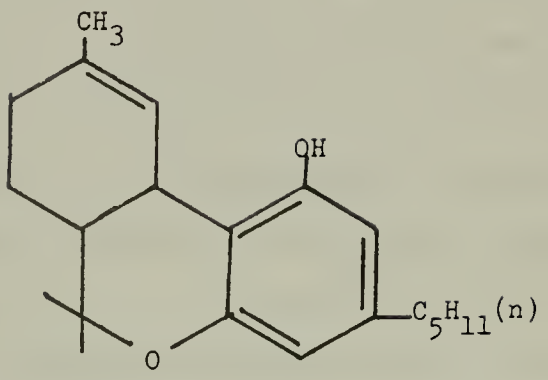
The term "cannabinoids" as generally used includes all the C_{21} compounds typical of and present in Cannabis sativa, their carboxylic acid analogues and their transformation products. In the last few years, intensive investigations have clarified considerably the rather complex chemistry of marihuana. Most natural cannabinoids in the plant have now been isolated and purified, their structures elucidated and analytical methods for their detection and quantification developed. In the period from 1963 to 1968, the true structure of the tetrahydrocannabinols was clarified and it was shown that a double bond in the synthetic tetrahydrocannabinol structure described in 1940 was in a different position in the natural tetrahydrocannabinol extracted from the plant. (9) At present, four major cannabinoids have been found in the plant: the two isomers:

(-)-trans-Delta-9 and Delta-8-tetrahydrocannabinols (Delta-9-THC and Delta-8-THC), cannabidiol (CBD) and cannabinol (CBN). Their formulas are shown in Figure 1. The major tetrahydrocannabinol believed to be responsible for the psychoactive properties of marihuana is the Delta-9-THC. Other minor cannabinoids present in marihuana include cannabigerol, cannabicyclol, cannabichromene and cannabidivarin. The structure of these compounds was determined by extensive use of modern physical techniques such as nuclear magnetic resonance spectroscopy, mass spectrometry, and, most recently, proton magnetic resonance. (2)

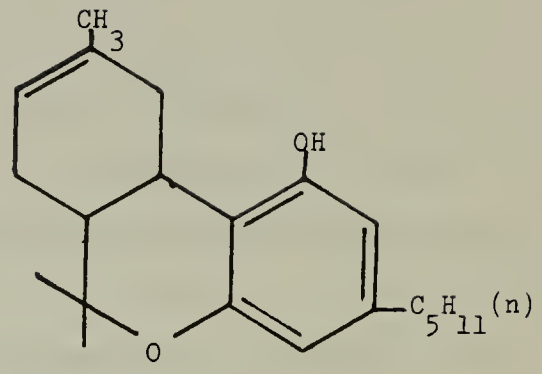
The nomenclature of the cannabinoids is rather confusing. As many as four numbering systems have been proposed and actually two different systems are used with about equal frequency. In one, the formal chemical rules for numbering pyran-type compounds are used because the tetrahydrocannabinols are substituted dibenzopyrans. In the other system, the cannabinoids are regarded as substituted monoterpinoids and numbered accordingly. Thus, the major constituent of marihuana is referred to either as Delta-9-THC or Delta-1-THC, and its isomer as Delta-8-THC or Delta-1(6)-THC.

In addition to the neutral cannabinoids described above, cannabinoidic acids have been isolated. (7) They differ from the neutral cannabinoids only in the presence of an additional carboxylic group in the molecule. Depending on the position of the carboxylic group in the benzene ring, two THC acids have been isolated: A and B. Rapidly upon heating, or slowly after storage, the acids can be decarboxylated to the corresponding neutral cannabinoids. In order to quantify the percentage of acids present in the plant by gas chromatography, a method was developed (PH-43-68-1338)

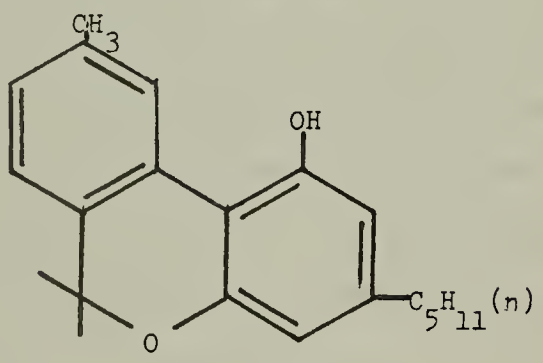
Figure 1



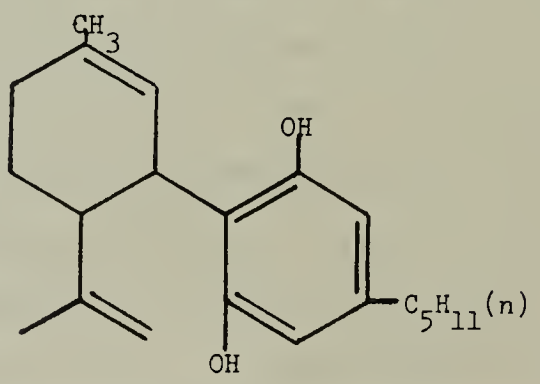
Δ^9-THC, Δ^1-THC
Δ^9-trans-tetrahydrocannabinol
Δ^1-trans-tetrahydrocannabinol



Δ^8-THC, $\Delta^{1(6)}$-THC
Δ^8-trans-tetrahydrocannabinol
$\Delta^{1(6)}$-trans-tetrahydrocannabinol



Cannabinol (CBN)



Cannabidiol (CBD)

which prevents decarboxylation of the acids in the gas chromatograph by transforming them to trimethylsylyl derivatives. Routine analysis of marihuana samples performed by NIMH (HSM-42-70-17) has shown that most of the THC (70-90%) contained in the fresh marihuana plant was in the form of acids. Investigation of the amount of THC acid at different times and in different parts of the plant showed that it is higher in the parts of properous growth and especially concentrated at the bractlet in the period when the seeds are at the peak of ripening.

Synthetic Material

Once Delta-9-THC became known as the principal psychoactive component of marihuana, a number of synthetic methods for producing it were proposed since extraction of THC from the natural plant material is both difficult and low in yield. However, they usually involved many steps and were long, tedious and expensive. Late in 1967, Petrzilka, in Switzerland published the first elegant and simple synthesis of Delta-8 and Delta-9 by condensation of trans-p-menthadiene (2,8)-1-ol with olivetol. (10) This method was further developed in the United States under NIMH contract (PH-43-68-1339) for larger scale production and has made possible the production of sufficient quantities of these materials to satisfy research needs. Methods of synthesis and analysis are being constantly improved and it is now possible to get 95% pure Delta-9-THC free of non-volatile material by rechromatography and redistillation. This better product contains fewer impurities than before and should prove to be more stable. The lack of stability of Delta-9-THC when exposed to air, light or increases in temperature has been one of the problems connected with the synthetic material.

These problems have not been encountered with Delta-8-THC since it is more stable and could be produced from the beginning in relatively pure form (98%). Limited amounts of the other cannabinoids such as cannabinol, cannabidiol and the 11-hydroxy-Delta-9-THC metabolite have also been synthesized and made available for research (NIMH contract PH-43-68-1452), mostly for use as analytical standards. Unfortunately, except for the cannabidiol which comes in a crystalline form, the other components of marihuana are oily, viscous materials both difficult to handle and to convert to convenient forms for administration. Ways are now being studied to make intravenous, oral and aerosol preparations which can be used in clinical studies (NIMH contract HSM-42-70-145). In view of the importance of the acids, they are also being prepared. As for the other marihuana components of research interest, depending on yield and available methods of synthesis, decisions will have to be made whether they should be extracted from the plant or made synthetically.

Extract

A material called marihuana extract distillate (M.E.D.) was prepared under contract by the National Institute of Mental Health (NIMH) in 1969 and contained 17% Delta-9-THC. Unfortunately, this extract was made from seized marihuana (before the NIMH started to grow its own product) and contained a large percentage of fatty acids not usually present in the plant. Extracts are now being produced under contract which contain as much as possible of the materials present in the fresh plant. The solvent used is usually petroleum ether and extraction is made at low temperature. The preparation of a standard marihuana extract and its testing is necessary

as long as there is not complete agreement on the fact that Delta-9-THC the principal component of marihuana, is the only one responsible for its behavioral effect.

Impurities in Marihuana

Although marihuana and the active ingredients of the hemp plant are the focus of this report, it must be recognized that other ingredients are sometimes found in the material that is smoked or ingested. Users are exposed to a wide variety of additives, diluents and contaminants, since marihuana is available only through illicit channels and systematic quality control is non-existent.

The frequency of a mixture of other psychoactive materials, whether of natural or synthetic origin, is not known. Nor is there any reliable information about the effect of these contaminants when present. It is clear, however, that an almost limitless number of compounds are available as possible contaminants ranging from deliberately added adulterants to inadvertent pollution by herbicidal action.

At the present time there are no means by which users can readily determine whether or not contaminants are present in marihuana. In direct contrast to drugs which have been diverted from legitimate channels with assurance of at least initial quality control, marihuana is always dependent upon the vagaries of the illicit distribution system for whatever purity it has.

Several reports give an indication of the magnitude of this aspect of the marihuana problem. Marshman and Gibbins present data from Ontario for 222 samples collected during the first eight months of 1969. The channels through which these samples were collected are not described. Of the 222 samples, it was claimed that 13% were hashish and 11% were marihuana. Of the total number of 222 samples, the composition was determined on 197 samples with 61.9% containing the drug that was alleged to be present. Of those samples alleged to be hashish, 100% were hashish; of those alleged to be marihuana, 67% contained marihuana.

The report states: "In regard to the 36 samples alleged to be marihuana, with a high cannabinoid content, 'good grass," as it would be termed on the street, some were marihuana cut with other substances and some contained no marihuana at all. Some of it appeared literally to be grass-lawn clippings; some of it looked like hay and smelled like hay. Our figure of 64 per cent for samples that 'contained marihuana' includes all the samples that contained any marihuana at all. It is clear that a sizeable portion of what is sold and smoked is not marihuana but other substances, sometimes of unknown origin."

A report by the Bureau of Narcotics and Dangerous Drugs' Laboratory Operations Division states that during the fourth quarter of fiscal year 1970, a total of 1645 exhibits of suspected marihuana were analyzed. Qualitative analysis showed negative results for 12% of the total or 191 exhibits. Even with use of a large number of specimens, the false positive claim rate fluctuated: 14% for the first quarter, 16% for the second quarter and 7% for the third quarter.

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EXTENT AND PATTERNS OF USE AND ABUSE

Background Considerations

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EXTENT AND PATTERNS OF USE AND ABUSE

Background Considerations

In order to discuss the scope of marihuana use the terms use and abuse should be defined. Use can be fairly easily defined as any consumption of parts or products of the cannabis plant that are believed to contain the active ingredient(s) or consumption of the active ingredients themselves. Use includes the act of smoking marihuana or hashish, the ingesting of marihuana or hashish incorporated into foods, the consumption in any manner of the active tetrahydrocannabinols or the drinking of infusion of marihuana or hashish which is believed rare in the U.S. at this time.

There is, however, no wide agreement on the meaning of the term abuse. Marihuana abuse has been defined at the most restrictive end of a continuum, as <u>any use</u> of the substance; at the most permissive end, as use that has resulted in serious adverse reactions of the individual. A middle position is that abuse is frequent, regular or chronic use, implying that habituation has occurred. It will be seen elsewhere that reliable figures on adverse reactions are not to be found; thus, it is not possible to give estimates of abuse in that sense. In many studies only the fact that someone has "ever used" marihuana was sought, making it unfortunately impossible even to distinguish frequent, regular or current use from past or present experimentation.

Most estimates of the scope of marihuana use rely on figures representing any use by the individuals in their lifetime; a few have looked at incidence, the use of the substance during a specified

time period, usually a year, or the time elapsing from the beginning of the academic year to the survey. The finer gradations have not been measured or reported in enough studies to enable one to make good estimates of use vs. abuse, regardless of the definition employed. Also, use of hashish has seldom been asked for or categorized separately from marihuana, so it is not known whether it should be included with marihuana or not.

Scope of the Problem: U. S. A.

The task of simply describing the scope of marihuana use in the U. S. has been and still is difficult. Some of the data needed for estimates simply do not exist. Those that do exist cannot be used with full confidence because they lack validity or reliability (or both).

The only sources of information on use by the nation as a whole are results of commercial polls (such as Gallup's) that included questions on drug use. Sources like these often are inadequate for reliable estimates of the scope of the problem. Gross measures of use are often the only basis for the figures. Information about methodology often is lacking, so that size of the sample, standards of interviewing, and the like, cannot be judged. Moreover, most surveys and polls on illicit drug use cannot guarantee that all responses to questions are valid. Studies to assess the probability of valid responses on this subject do not exist.

Other than nationwide polls, the sources for estimates consist mainly of one-time studies of high school and college students conducted in scattered locations, with varying quality of sampling techniques, instruments, and survey methods (3). Recently, however, a handful of studies have

been repeated for the second and third years, so that changes in drug use in those locations can now be gauged more reliably (26, 22, 20, 12).

The first nationwide survey of college students by any Federal agency (NIMH grant 16536-01) has just completed the tabulation of preliminary data. This study of 10,000 students at a sample of fifty colleges across the country was conducted by Dr. Peter H. Rossi in the Department of Social Relations at Johns Hopkins University (27).

Problems in Obtaining Accurate Estimates

Assessing marihuana abuse has special difficulties beyond the ordinary precautions for assuring statistical reliability and validity. The reluctance of drug users to admit to illegal behavior in interviews or questionnaires can reduce the estimates below the true figure. On the other hand, in certain situations, young students may use the opportunity to pretend higher use, inflating the estimates. In order to improve the probability of valid responses, it is advantageous to offer respondents confidentiality or immunity from prosecution. (In extreme cases, researchers too have been subject to subpoena of their records or of their knowledge of illegal drug use by respondents). Until November 1970 there were few States that protected confidentiality (New York was one) or provided researchers immunity (Massachusetts and New Hampshire were two).

Another difficulty arises in attempting to collect data in classrooms. Many principals and boards of education are opposed to use of the school day for this purpose or do not wish to risk parental disapproval. In

many schools parental approval must be obtained for any testing of pupils. Finally, permission to survey a school population is often denied from fear of the adverse publicity that might result.

Estimates of Marihuana Use

In October 1969, Gallup reported results of a poll of a sample of adults 21 years and older in the United States that indicated that 4% of these adults had used marihuana at some time (11). It was estimated that the total number was about 10 million. At about the same time, the Director of the National Institute of Mental Health testified before a Senate Subcommittee that eight to twelve million persons in the United States had some experience with marihuana (31). The Gallup Poll indicated that use was more common among younger than older persons: 21-29 years (12%); 30-49 years (3%); 50 and over (1%). Also, the poll showed that men tended to use it more than women (6% vs. 2%). Those with college background had a higher use rate than those with a high school or grade school background (9% vs. 3% vs. 1%), and the West and East regions had higher rates than the South and Midwest (9% West and 5% East vs. 2% South and Midwest).

Preliminary data from a 1970 nationwide survey of college students indicates that 31% of the students have used marihuana at some time; 14% of the students had used it every week or two during the semester in which the self-administered survey schedules were completed (27). Compared with the Gallup figures for 1969, it indicates a substantial increase among college students; this comparison, however, can only be rough because of possible differences in methods and sample sizes used in the two surveys.

Nationwide surveys of college and high school students now in progress (27,9) cannot yet show whether student rates of marihuana use differ by region as adult rates apparently did in 1969 (11). Since the separate studies of schools and colleges vary so much in geographical coverage, sampling, method of administration, and other conditions of data collection, comparison of their rates by region is not warranted. Until 1969, few if any studies were made in the Midwest of South, so knowledge of the problem was heavily influenced by studies made on the West and East coasts.

Nevertheless, the studies that have been done in the Midwest since 1969 hardly indicate that rates are any lower there. A Michigan study of eleven high schools in 1969 showed that rates varied from none to 34% of students in selected schools who had "ever used" marihuana (6). In the same year, the rates were 12% in one Utah study and 23% in a Wisconsin study (13,30). One college study only, at the University of Michigan in 1969, revealed a rate of 44% who had "ever used" marihuana (10). These rates are at least as large, and some are larger, than rates found in some studies in other parts of the country.

The fact that marihuana use had been increasing up to 1969 has been indicated by several surveys that were repeated the second and third year or in the same location. In all of these surveys, the use of marihuana increased five to twelve percentage points between 1968 and 1969. This increase occurred in the secondary schools in San Mateo County, California (26); at the University of Maryland (20) at Carnegie-Mellon University, Pittsburgh (12), and among college students nationwide (22). Undoubtedly, increases would have been found in almost every school or college during that period.

There is just one study capable of indicating high school trends for 1970, but it shows an interesting change. For three years, San Mateo County in California has conducted a survey of drug use in the junior and senior high school grades (26). In 1970, a total of 35,145 students were surveyed. In both survey years 1968 and 1969 there were steady, large increases in marihuana use. The increase in 1970, however, was decidedly smaller. For boys, instead of the average 7.9 percentage point increase in "any use" between 1968 and 1969, there was an average of 1.6 percentage point increase between 1969 and 1970. For girls, the increase was greater, but there was a definite lessening of the former rapid increase. An average increase of 7.2 percentage points from 1968 to 1969 declined to a 3.4 percentage point increase in 1970.* The average proportion reporting use within the past year was 42%, a high rate among the schools surveyed.

Even more important than the apparent lessening of the rapid increases in marihuana use in the high schools, the seventh and eighth grade classes in San Mateo actually showed a decrease in marihuana use between 1969 and 1970. In every category of student by age, grade, and sex, the reported use of marihuana had declined slightly from the previous year's figures.

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*These changes are not a function of a statistical "ceiling effect" that sometimes results when there is little room for figures to change. The proportions having had "any use" during 1970 ranged from 32% to 51%; at these levels, there was sufficient room for large increases, but they did not occur.

Changes in use of marihuana in one county's schools cannot represent the situation generally in schools across the country, of course. Undoubtedly, in many schools and colleges there will continue to be increases in use, and rapid increases. However, schools on the West Coast were the first to experience the onslaught of drugs, and there is some reason to expect that their experience may presage a stabilization of rates or possible decline in interest among students.

Use by Individuals Other than Students

If there is now the beginning of a lessening in student drug use, it may be outweighed by increased interest in marihuana on the part of out-of-school young adults. A study of marihuana use (one or more times) by adults 18 years and above in San Francisco in 1969 indicated that almost the same proportions (about 40%) of non-college young adults as college students of the same age groups had used the drug (16). The rate of use by all adults 18 years or older in San Francisco in that study was 13% (17).

By way of comparison to student studies and to studies of adults of all ages, figures below can be given for certain other groups which were studied separately (3).

High school dropouts who had ever used marihuana in a study in Utah in 1969 made up 50% of the group. In another study, marihuana users made up 26% of a group of employed youths 16 to 23 years old. Three studies have been made of marihuana use by servicemen, two conducted

with soldiers in Vietnam. In the most detailed report, 32% of the servicemen in Vietnam had used marihuana at some time, three fifths of the users had done so twice since coming to Vietnam. In another study, 23% of enlisted men on active duty in 1969 had used marihuana (4). Forty-seven percent of Negro men who had grown up in St. Louis had tried marihuana at least once by the time they were in their early thirties (24).

Studies of hippie communities consistently show 95% to 100% who have used marihuana (3).

Gradations of Use

It is recognized that gross estimates of marihuana use cover a number of gradations on several dimensions. Where frequency has been determined, it has been found that many users have used once, and only a portion have used more than 10 or 20 times. Where current usage (i.e. prevalence) has been determined, it has been found that only a portion who ever used were doing so at the time of the study. Another dimension that has not been measured but undoubtedly varies for many users is the regularity with which the drug is used. In 1969 the Director of the National Institute of Mental Health testified that about 10% of all users of marihuana were chronic*users and about 25% occasional users (31). The remainder were "tasters" or one-time users. On the basis

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*In this instance "chronic use" is a loose concept covering all use at the upper levels of frequency, regularity, or both.

of those percentages, it was estimated that there were 800,000 to 1,200,000 chronic users of marihuana in the nation at the time, and 2 to 3 million occasional users.

Other studies have produced breakdowns resembling the 10% chronic, 25% occasional, and 65% experimental distribution, but the categories differ. In 1969 in one high school study and one study of nine campuses about 40% of those who had ever tried marihuana had ceased using it (21,1). In a study of over 5000 enlisted men on active duty, about 60% of users had used it ten times or more (4). Among servicemen in Vietnam, 76% of users had experimented or used it twenty times or less (25).

In the nine-campus study, there were relatively more experimenters in the older group of students, and more moderate or heavy users in younger groups.

The question of how long a person might use marihuana at the various gradations of use cannot be answered yet. One comment from an observational study of drug using groups of young peers was that most youth even when using marihuana daily tend to pass through the drug scene in about a year (29). After the stint in the subculture, however, they may still use marihuana occasionally.

Socio-demographic Characteristics of Users

Some indication of the identity of marihuana users nationwide was found in the Gallup poll results of 1969, mentioned above. In addition,

marihuana studies on campuses and in high schools provide a fairly consistent picture of the characteristics of users (5,28,6). It should be kept clearly in mind that these characteristics are only associated statistically with marihuana use and do not imply causation. Single males are three times as likely to use marihuana as single females or married persons of either sex. Users tend disproportionately to be from upper income or professional families. Those who are not affiliated with a formal religion are more likely to have used marihuana. They tend to major in arts, humanities, or the social sciences rather than in other fields. More than non-users, they have dropped out of school at some point. They participate less in campus organizations or activities except political ones.

Most of these findings were from studies done in 1968 and 1969. It is a distinct possibility that as more students try marihuana the differentiating characteristics noted in early studies will be less pronounced. This is a phenomenon that occurred with respect to drinking and smoking in past years. The more widespread the practice became the less deviant were the practitioners as a group.

Approximately the same pattern of socio-demographic characteristics is found among high school users of marihuana. In addition, it has been found that they are more likely to date steadily and start dating earlier than non-users. Again, the association is statistical and does not imply that marihuana use leads to earlier dating. Among high school students in one study, marihuana use or interest in use was related to

college plans: the college-oriented were also marihuana-oriented (19).

Student marihuana use also varies by type of college or school, along the lines suggested by the nature of users (1). Colleges whose students have higher socio-economic backgrounds, such as private colleges or universities, tend to have higher rates. (Women's colleges are exceptions.) Large public universities also have fairly high rates, as well as liberal arts colleges, except the small denominational schools. Schools with a professional, vocational, or technical program tend to have lower rates. In the nine-campus study in the interior of the country in 1969, the following rates of marihuana use were found for the different types of colleges:

Medical center	20%
Large private university	16%
Large State university	16%
State commuter college	12%
University commuter branch	11%
Nursing school	11%
Small male technical college	7%
Small denominational women's college	7%
Small denominational men's college	7%

High schools follow a similar pattern: Private schools and urban and suburban schools have higher rates of use than small town and rural schools.

The Hang-loose Ethic

Certain attitudes and interests have been shown to be even more closely related to marihuana use than are the socio-demographic characteristics (28). None of these attitudes was true only of

marihuana users, nor true necessarily of all of them. And there is no indication that marihuana use caused them. Characteristics of the hang-loose ethic have been defined as: dissatisfaction with own education and the system; opposition to the Vietnam war and the draft; approval of sexual freedom; feeling a communication gap between self and parents; anticipation of satisfaction from future leisure activities more than from work; participation in "happenings" and mass protests; interest in underground newspapers; and belief in possible circumvention of laws (but not necessarily in breaking them).

High school marihuana users attitudes tend to be similar. In high schools, however, marihuana use appears to be more recreational than symbolic of positions on politics and life (6).

Initiation and Source of Supply

Few detailed data are available on initiation in a group of drug users or source of supply of marihuana. In several studies, however, it appears that most users are introduced by a close friend or someone they know well. In one college study, most began use in a friend's apartment with one or two others present (12). In one high school study, students most often obtained the drug in other people's homes, and about half obtained it without spending money (14).

Before the rapid spread of interest and use in marihuana in the 1960's, the sociologist Howard Becker described the process of becoming a marihuana smoker (2). In essence, the initiate seldom experiences

any effects of the drug in the beginning without instructions from associates on how to inhale and hold the smoke in the lungs. The individual's interpretation of the experience as euphoric and sociable is aided by the expectations of the group.

Marihuana Use in Other Countries

Cannabis grows in most of the countries of the world, including all those in the Western hemisphere, Africa, the entire continent of Asia, Australia and the Indonesian archipelago. A few scattered varieties may be found in Europe. Although there are botanical affinities between the various subspecies of cannabis sativa, the amount of psychoactive components in the plant varies widely.

The use of the plant for medical and religious purposes probably predates its use as a recreational drug. Cannabis has played a medical role in every country in which it was grown, including the United States, where from colonial times until at least the second decade of the present century, it was used in the treatment of a variety of illnesses. Until 1937, marihuana in some form was a staple in many U. S. patent medicines. It is still used in Arabic and Indian medicine, and in the United Kingdom may be prescribed by doctors in the form of an extract or tincture of cannabis. According to the 1968 report on cannabis by the Advisory Committee on Drug Dependence, medical use by doctors is increasing in Britain. (7).

In many countries cannabis has been used for religious purposes, either in conjunction with certain ceremonies (where use is presumably not continuous) or to aid in meditation and the attainment of certain

mystic states (particularly in India) when use would be presumably more constant, and the actual amount of the drug consumed much greater. The Indian Hemp Commission Report examined the use of cannabis in various parts of India, by various religious groups, and two later published reports have expanded on the original material (18). Religious use of cannabis has been noted among primitive groups in Central and South Africa, Brazil, Mexico and Jamaica.

Despite the thousands of years cannabis has been used for medical, religious and recreational reasons, and in spite of its practically worldwide distribution as a growing plant, there are no accurate figures available on a worldwide basis of the amount of marihuana consumed (and in what form), how much goes into medical and how much into non-medical channels, the number and kinds of users, and the modal frequency of use. Moreover, the quantity and quality of reporting in this field varies widely from country to country, depending, as it does, not only on the method of data collection and the sources from which that data is collected, but also on the perceived threat to the society of cannabis use, and the history of its use in discrete and disparate segments of the population.

In 1956, the United Nations Commission on Narcotic Drugs observed that it was clear that the consumers of cannabis, as of opium, numbered over 200 millions in the world, and that geographically it was the most widespread drug of abuse. Actual hard figures as to prevalence and incidence are notoriously lacking, however. Most countries rely on figures of arrest and customs seizures to indicate the extent of the

problem, and these figures, of course, depend on the size and training of the enforcement patrols, general public interest in the problem, and a host of other variables. It can certainly be said with confidence that these figures underrepresent the total amount of marihuana consumed, as well as the number of users. In India, government excise records provide the most accurate statistics on the amount of cannabis consumed.

The Wootton Subcommittee of the British Advisory Committee on Drug Dependence received estimates from witnesses concerning the number of people who had tried cannabis and those who used it regularly (7). Estimates of the number of British users ranged between 30,000 and 300,000 and the Commission itself could find no firm basis for issuing an estimate of its own. They did publish a list of convictions for cannabis offenses from 1945 on, and their figures show a steady progression from 4 in 1945 to 2393 in 1967. In 1966 and 1967 there was an annual doubling of convictions, but Commission members doubted that these figures represented an actual increase in amount of cannabis consumption and suggested they were possibly due to increased police vigilance.

The type of cannabis offender also changed markedly from the 1950's (when the first use of cannabis was noted among non-white immigrants to England) to 1964 when, for the first time, white persons constituted the majority of offenders. This trend has continued. The Commission concludes that, on the basis of convictions alone, cannabis use is not only widespread geographically, but cuts across class and color lines as well.

Many witnesses felt that it was possible to distinguish various types of marihuana users, for example, college and university students, jazz and pop musicians and artists, people working in the mass media, professionals in a variety of fields, as well as a growing number of workers in unskilled occupations - however, none of these witnesses could give anything but an informed guess as to the actual number of people involved in these various groups.

Although the Wootton Subcommittee Report mentions the fact that an increasing number of doctors are prescribing extract of cannabis and tinctures of cannabis, they give no exact figures as to the number of prescriptions, the number of doctors prescribing, or the amounts prescribed. At the time the report appeared, there was no requirement that prescription records should be available to the Inspector of Drugs, but Commission members felt that such records should be made available in order to keep a close watch on the prescribing trend within the next few years.

In Ireland, there are no complete studies either from private or official sources relating to drugs and drug abuse. There is, however, a Working Party on Drug Abuse established by the Ministry of Health in December of 1968, and they have released some figures on drug abuse in the Dublin area. A press release from this Working Party (June 2, 1970) indicates that there are at least 350 young people who have abused drugs, and the number is increasing. The drugs involved to date have been mainly amphetamines, barbiturates and tranquilizers (usually stolen,) and LSD and cannabis smuggled into the country. An outpatient center

for drug abusers has been set up in Dublin at the Jervis Street Hospital.

In July 1970, the German Federal Ministry for Youth, Family and Health was given a 1971 budget of approximately $375,000 to carry out a program of intensified efforts to prevent a rise in drug abuse (primarily hashish and marihuana). German authorities state that they did not, until comparatively recently, have a drug abuse problem, and they still do not have much of a problem with the hard narcotics. Illicit use of heroin and opium is virtually unknown.

Part of the funds budgeted for the Federal Ministry will be used to conduct at least two surveys - one survey, to be conducted by the Federal Center for Health Information, will attempt to determine pattern of use and motivation for use in sample of 300 persons aged 15 and over. The second survey will be conducted among 5000 school children. The Bonn Government has also requested aid from other countries (including the U. S.) to help them in developing effective programs of prevention, education and treatment in the drug abuse field.

In Austria, the growing amount of drug use by juveniles is a major concern of the Federal Ministry of Education and Arts. In the Spring of 1970, the Ministry initiated a survey of school authorities in Austrian schools (excepting elementary schools and those for the mentally retarded) to find out how many cases of drug use had come to their attention. Although the final reports of this survey have not been published, it was apparent that hashish was the drug of choice for most students.

Sweden in 1968-1969 conducted, through its Military Psychological Institute, an extensive study of 23,305 eighteen year old military conscripts to investigate their use of drugs, including tobacco and alcohol. The study (which guaranteed anonymity to the respondents) was undertaken in four major recruiting areas. Fifty per cent of the boys in the study came from big city areas.

In large city areas about 19-26% of the conscripts had used illicit drugs at least once, and for smaller cities the rate was between 8% and 9%. For drug experienced conscripts (defined as someone who has used a drug at least once) cannabis is by all odds the drug of choice, at least 58-73% of the conscripts have used cannabis from one to ten times, and cannabis is the favorite drug for 74% to 91% of them. The first drug tried, for about 77% to 89% of the users, was cannabis. Between 25% to 60% of those who have not tried illicit drugs have been offered them one or more times.

In Australia, according to a New York Times dispatch, December 20, 1970, the Minister for Customs and Excise states that they have seized twenty times more drugs this year than two years ago. Surveys by the narcotics section of the federal police department have shown that students account for 6 to 8 per cent of defendants charged with drug offenses, members of the armed forces 2.3 per cent. The bulk of the offenses were committed by unskilled and semi-skilled workers in their early twenties. Marihuana was involved in 44% of the drug cases brought to court this year - an increase of almost 13% in such prosecutions

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since last year.

In New Zealand, a special committee set up in 1968 under the Board of Health, made its first report in February of 1970 on Drug Dependency and Drug Abuse in New Zealand (8). The Committee indicated that they were not in a position to give a full and comprehensive picture of total cannabis use in New Zealand, but that on the basis of evidence obtained during the course of extensive public hearings they were prepared to state that at least four groups of users could be identified. These groups included: Multiple drug users (those who combined cannabis use with the use of other drugs), cannabis only users, spree or occasional users, and experimental users. Since cannabis is only intermittently available in New Zealand, this was not the drug of initiation for many of the drug users whom the committee interviewed. Drug use seems to be concentrated more in North Island than in South Island. Cannabis seems to have been introduced to New Zealand early in the 1940's by American service men, but did not seem to catch on to any extent until the early 50's, when it was taken up by people in the entertainment industry. In the 1960's other segments of the population became involved and members of the Commission believe that use, while still not extremely extensive, so far as they could determine, is now spread through varying segments of the population.

In Canada, the Interim Report of the Commission of Inquiry Into the Non-Medical Use of Drugs (the Le Dain Report) gives the results of high school and college surveys on cannabis use (15). In eleven high school surveys conducted in various parts of the country in 1968 and 1969,

admitted cannabis users (defined as those who had used the drug at least once within the past six months) ranged from a low of 5.9 to a high of 24.2%. In the largest of these surveys (N of 11,454) conducted in 1968 in London, Ontario, the usage rate for males was 7.9 and for females 3.6%.

College surveys carried out in 1968 and 1969 at six universities ranged from a low of 19.6% use to a high of 44.5%. In general, surveys carried out in 1969 show a higher use rate (use defined in the same way as in the high school surveys; i.e., use at least once within the past six months) than those conducted in 1968. One survey, carried out in the fall and spring terms of the same academic year, is of particular interest because it shows a rise in percentage of users from 19.6% to 27.3%.

The Commission, on the basis of these published survey studies, as well as testimony gathered from expert witnesses, and data from government and police records, states that it is reasonable to believe that probably more than 10% of all high school students in Canada have used cannabis, and, of course, some studies in certain parts of the country have found much higher proportions. Data on use from a university level suggest that at least 25% of all university students have at least experimented with marihuana.

The Commission solicited, and received, letters from private citizens on the non-medical use of drugs. A review of these letters, as well as expert testimony from informed observers, indicates that the use of cannabis has spread to groups other than the young in various social classes.

Although the New World has a much greater array of both narcotic and hallucinogenic plants than the Old World, cannabis is not indigenous here. The plants were probably introduced at the time of the Spanish conquest to Mexico, Central and South America. There is a difference of opinion among experts about Brazil, with some persons claiming that cannabis was introduced by the original Portuguese explorers, and others who state that it came in later, with the advent of Negro slaves. In some of the islands of the West Indies (Jamaica, Trinidad) cannabis (ganja) was brought in by East Indian indentured laborers after the emancipation of the Negro slaves. In the United States, most writers feel that cannabis (in the form of the hemp plant) was introduced by the early English colonists.

There are few adequate use figures from any of the Latin American countries, but unpublished reports from the Pan American Health Bureau, as well as other informed sources, agree that the same phenomenon observed in other parts of the world, i.e., the spread from exclusive lower class use to use by at least the younger members of the middle and upper classes is increasing. These reports are particularly interesting in view of the fact that in Latin American countries the difference in life style between members of the lower classes and those of the upper class has always been much greater than that which prevails in more highly industrialized and urbanized countries.

The growing amount of multiple drug use by middle and upper class youth has prompted interest on the part of public health authorities, and they have asked for expert assistance from the United States in the design of survey studies to be used with school populations.

Brazilian scientists have long had an interest in cannabis use, as is evidenced by papers presented at the second Pan American Scientific Congress held in Washington in 1915. Present day research interest spans the physical and the behavioral sciences.

Up until the beginning of rapid industrialization in southern Brazil about two decades ago, use of cannabis tended to be centered in the northeastern coastal states, and in cities with a high concentration of Negroes such as Bahia. Poor immigrants from these regions to Sao Paolo and Rio de Janeiro brought maconha with them when they decided to hunt for jobs in the fast growing industries. Present day reports indicate that use has spread from these impoverished workers to young members of the middle and upper classes.

Reports emanating from Lima indicate that there is a growing use of drugs of all types, primarily by young middle and upper class students. However, there is one interesting footnote which should be appended - in the Lima squatter settlements with inhabitants drawn mainly from the high Andes, there is evidence that coca is being replaced by cannabis as the drug of choice. Such self-medication, i.e., the substitution of cannabis for a stronger drug, has been noted previously in other parts of the world, for example, India, where cannabis has been used in place of opium.

In Mexico, where use of marihuana has long been common among both the rural and the urban poor, authorities indicate that use is now spreading among wealthy youngsters, as is indicated by the growing number of arrests in this group.

Cannabis is an illicit drug in all Latin American countries, but most drugs which can be obtained only on prescription in the United States (sedatives, amphetamines, tranquilizers) can be bought over the counter in most countries there.

In the Caribbean, marihuana (ganja) was introduced by East Indian laborers after emancipation. An NIMH sponsored study of chronic cannabis users in Jamaica indicates that they are drawn from at least five disparate population groups. Up until about three years ago users were predominantly members of lower class rural and urban groups, but authorities report that middle and upper class youngsters are now increasingly turning to use of the drug. One group of users in Jamaica, the Rastafaris, are of particular interest, since a good deal of their religious ritual as well as life style revolves around the drug. These people call themselves "the chemists of the divine herb" and use ganja in all forms, from both male and female plants, in foods and for smoking. Ganja is even used in a concoction especially designed for babies with croup.

Cannabis use was widespread in Near Eastern, African and Asian countries for a much longer period of time than in Western countries, so

the literature is much more extensive from these regions. However, several cautions should be borne in mind when considering these studies. These cautions include: 1. The use of biased samples (study groups frequently drawn from prison populations, or exclusively from members of the lowest economic groups); 2. The lack of adequate control groups; 3. Frequent failure to consider the implications of the fact that cannabis tends to be mixed with other drugs (tobacco, dhatura, or more rarely opium), or the corollary question of the extent to which users of cannabis are also users of other drugs.

The question of the duration of use of cannabis is probably one of the most important issues from a public health standpoint. Observations of Eastern writers tend to be at odds with those from other parts of the world. Most of the former imply that once the cannabis habit is established it is likely to last as a daily habit for many years. However, actual longitudinal data on representative samples of persons initiated to its use are seldom if ever cited. In other parts of the world there are indications that there may be discontinuation with some users after adolescence, and with others the establishment of a pattern of intermittent use.

The government excise records of India afford the most accurate statistics on the amount of cannabis used in that country, but it must be recognized that there is no adequate estimate of the amount of material which enters the country illegally, primarily from Nepal. It is estimated that the current number of habitual ganja users is about 240,000 (not including the users of bhang, or of smuggled charas). This is about one

half of the number of licit ganja and charas users (excluding bhang) estimated in 1940. Most observers feel that the steady decline in cannabis use in India can be attributed to several factors, including a reduction in the number of acres licensed by the government for production, higher excise duties, increasing competition from other drugs, and a growing belief that cannabis is essentially a low status drug.

Although the decline in cannabis consumption in India is striking, there is some evidence that India is not immune from the rising use of multiple drugs by students, which is characteristic of many other countries.

In Egypt, expert observers estimate that the current number of hashish users is about 180,000, which would include aboust four to five percent of the male population between 20 and 40.

There are no adequate current use figures from Morocco, but most trained observers estimate that about 30 to 35% of the adult male population use cannabis to some degree.

There are not even estimates available for South Africa after 1953. In that year the estimate of users was about 50% of the native male population in some areas, but relatively low in others.

There are no estimates at all available for the number of users in Nepal, the only country in the world where cannabis use is legal.

The foregoing brief summary of cannabis use in countries other than the United States points up the general inadequancy of the data currently available on extent, patterns, and persistence of use, the physical and psychological characteristics of users, as well as the general social climate in which cannabis use is either introduced, expands, or declines.

Research into the relative frequency of the various patterns of cannabis use in differing cultures is badly needed, as well as longitudinal studies with user groups in certain selected countries, and carefully designed small studies which will examine in depth natural history of drug using careers.

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PRECLINICAL STUDIES IN ANIMALS

Toxicity Studies

Central Nervous System Effects

Autonomic and Cardiovascular Effects

Effect on Respiration

Hypothermic Effect

Hormonal Effects

Antibiotic Activity

Interaction with other Drugs: Biochemical Studies

Neurophysiological Effects

Behavior Effects

Teratology

Metabolism

The following section summarizes a wide range of animal investigations designed to learn some of the implications of cannabis administration in a variety of animal species. It is included primarily for the technically sophisticated reader as a summary of the present state of marihuana preclinical investigation. It should be emphasized that such research may have no immediate relevance to human use of marihuana, and that it could be a serious error to attempt to translate directly these findings to the human case. High dose levels are frequently employed in animals to learn the limits of toxicity (not possible in human experimentation). Moreover, the methods of drug administration (and form of the drug) are often markedly different from the usual ways in which marihuana is used by people and may have different implications. Nevertheless animal work is essential to a more sophisticated understanding of the action of the drug and to developing useful clues to fruitful lines of investigation in man. Where specific findings appear to have direct relevance to human use of marihuana, an attempt has been made to interpret this in the summary or in other relevant sections of the report.

PRECLINICAL STUDIES IN ANIMALS

Prior to 1968, research on the effects of cannabinoids in animals was carried out with cannabis extracts prepared by the investigator himself and such preparations frequently lacked definite analysis of their active

components. This has made it difficult to correlate physiological effects with chemical composition in the earlier studies. Recently, the availability of pure Delta-9 and Delta-8-THC has spurred research in the pharmacological area and so far, pharmacologic effects of the tetrahydrocannabinols seem to generally replicate, at least qualitatively, those of the cannabis extracts.

1. Toxicity Studies

Single dose toxicity studies in rats indicate that the lethal dose in 50% of animals, i.e. the LD_{50} for Delta-9-THC, is between 20-40 mg/kg by intravenous injection, and between 800-1400 mg/kg orally, depending on sex and species (66, 59). Animals receiving these compounds at these very high dose levels die in respiratory arrest. Postmortem studies done after treatment with marihuana derivatives revealed pulmonary edema with hemorrhage (49).

Tolerance to cannabis action has been reported in a number of animal species (rats, dogs) and in birds (pigeons) (52). In 1968, using behavioral methods (rope climbing, operant behavior), Carlini showed that seven out of ten rats became tolerant after fifteen chronic, intraperitoneal injections of cannabis extract (20). However, there was no cross-tolerance between cannabis extract or Delta-9-THC and LSD-25 or mescaline sulfate. This seems to indicate that tolerance to cannabis must involve a different mechanism from that of LSD or mescaline, since cross-tolerance has been established for the two latter drugs. Among the cannabinoids, cross-tolerance has been found between Delta-8- and

Delta-9-THC (53), between the cannabis analogue, synhexyl and Delta-9-THC, and between the dimethylheptyl analogue and Delta-9-THC (9). Tolerance has been found in dogs but not in rabbits (48). Tolerance to Delta-9-THC in dogs can be blocked by prior administration of an enzyme inhibitor, such as SKF 525A. Thus, research on comparative metabolism between different species and enzyme induction studies may provide a clue to these species differences.

2. Central Nervous System Effects

Reports on the effects on the brain and the nervous system, sketchy at first, are now the subjects of various investigations. (Effects on the electroencephalogram are reported under Neurophysiological Effects.)

In animals, analgesia has been the most frequently used parameter of cannabis effects. Bicher and Mechoulam (8) have assessed this effect in mice for both Delta-8 and Delta-9-THC, by the hot plate and tail flick tests. Twenty milligrams per kilogram of either isomer, intraperitoneally, was found to be equivalent to 10 mg of morphine given subcutaneously, and the analgesic effect of the tetrahydrocannabinol lasted at least two hours. Others have reported that Delta-9-THC is a more potent analgesic agent than Delta-8-THC (41). A combination of morphine (2-4 mg/kg) and THC (1.25-5.0 mg/kg) was found to possess additive analgesic effects (19). It was also noted that drugs which decrease serotonin brain levels do not modify THC analgesia.

In 1965, Carlini and Carlini (23) compared the effects of cannabis extract (10 or 100 mg/kg) i.p., and strychnine on the content of RNA and DNA in the rat brain. Cannabis had no effect on RNA content of rat brain but significantly increased DNA content in a dose related manner (12% and 82%, respectively). Changes in DNA content may be involved in the short term memory deficits reported in humans.

In terms of effects on biogenic amines, cannabis resin was found to increase serotonin brain levels in mice (43) and rats (12). Norepinephrine in mice, 24 hours after i.p. injection, was found to be decreased by 5-10 mg/kg Delta-9-THC, but significantly increased by doses of 200-500 mg/kg. These changes in biogenic amines may be due to a direct central effect or the result of peripheral effects of marihuana.

3. Autonomic and Cardiovascular Effects

Hashish resin extract had been reported (12, 13) to antagonize acetylcholine induced contractions of rat uterus and intestine in a dose related manner. In the same experiments, serotonin activity was also antagonized.

Reports of the effects of cannabis on the adrenergic system are controversial. Some (12) report that cannabis resin antagonized adrenergic effects such as the pressor response to occlusion of the carotid artery in dogs, the positive inotropic effects of epinephrine and norepinephrine in isolated frog heart and the action of epinephrine in the rabbit duodenum. This inhibition of the pressor response is not

due to ganglionic blockade (26). Others have found that both Delta-8 and Delta-9-THC potentiate all parameters of norepinephrine and epinephrine and that Delta-8-THC is more potent in reversing reserpine induced blepharoptosis in mice. Cannabis resin also antagonizes the spasmogenic actions of carbachol, histamine, barium chloride and pitocin on rat and guinea pig intestines by a direct musculotropic effect (13). Dewey et al (26) confirmed this inhibition in isolated guinea pig ileum, remarking that the Delta-9-THC block is reversible, while Delta-8-THC is not. They found the Delta-9 isomer nearly twice as potent as Delta-8-THC in inhibiting GI propulsion in mice in vivo.

Marihuana compounds (Delta-8 and Delta-9-THC) produce a gradual, prolonged fall in blood pressure (34, 27), but the synthetic analogues such as the dimethylheptyl may be more potent in this respect (24, 25). This hypotensive effect is not dependent on an intact vagus nerve, is not diminished by atropine, dibenamine or hexamethonium and is not due to ganglionic blockade (27). This effect can be abolished by spinal section at C-1, at least with EA1476, a 1,2 dimethylheptyl derivative of THC (40). The cardiovascular responses to direct stimulation of the hypothalamus and medullary vasomotor areas are not blocked by EA1476, so it is postulated that this hypotension results from decreased central sympathetic outflow.

In the isolated, perfused rat heart Manno,et al (50) have found that, as the dose of Delta-9-THC is increased, perfusion pressure is also increased (vasoconstriction) but the force of contraction is

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decreased. For both of these effects, no definitive dose-response relationship could be defined.

4. Effect on Respiration

Cannabis usually depresses respiration rate, at least in moderate to high doses (33, 34), although stimulation has also been reported (13). As mentioned earlier, toxic doses produce breathing impairment.

5. Hypothermic Effect

Doses of Delta-9-THC greater than 1 mg/kg have been found to consistently produce hypothermia in mice, and 500 mg/kg lowered the body temperature by 5-6 degrees within 10 minutes after i.p. administration. This effect usually lasted 24 hours (43). Marked hypothermia was also observed after intercerebral administration of cannabis extract (33).

6. Hormonal Effects

In rats, cannabis extract (250 mg/kg, i.p.) given prior to injection of I^{131} in rats, significantly depressed thyroidal uptake of the radioiodine (54).

The effect of cannabis on blood sugar is not established. Miras found a biphasic fluctuation of blood sugar within normal limits, but El Sourogy (28) using an extract of cannabis, found a significant increase in blood glucose, while liver glycogen was decreased and muscle glycogen remained normal, suggesting potentiation of glycogenolysis. Unfortunately, there was no mention of control animals receiving injections, so the possibility remains that a stress response was being measured.

Barry, et al (6) have found activation of pituitary-adrenal function in rats following 4-16 mg/kg i.p. , Delta-9-THC, probably resulting from a central nervous mechanism for hypersecretion of corticotropin, since corticosterone levels sometimes triple following THC but do not after hypophysectomy, pentobarbital or morphine. Inhibition of antidiuretic hormone was also indicated in view of the doubled urine output; these two effects also occur following alcohol intoxication.

7. Antibiotic Activity

Cannabis preparations have long been known to possess antibiotic activity against gram positive bacteria in vitro or in topical administration; recently, this activity has been narrowed down to the cannabidiol fraction of the plant (60).

8. Interaction With Other Drugs: Biochemical Studies

So far, few authors have reported on the interaction of cannabis with other drugs. The only interaction which has been well reported is the interaction with barbiturates as those compounds were used to determine the effects of THC on the central nervous system. Natural (extracted), synthetic THC and synhexyl (a synthetic analogue) have been shown to potentiate hexobarbital and barbital sleeping time (35, 46). However, the mechanism of this potentiation, possibly through enzyme induction, is still debated. The results of Truitt showing decreased sleeping time in mice when the animals were pretreated twice daily for three days with Delta-8-THC (3-30 mg/kg, i.p.)

then given 65 mg/kg pentobarbital, seem to support the enzyme induction theory (NIMH contract PH-43-68-1338), but others question it.

Potentiation of amphetamine has been noticed after administration of cannabis compounds both acutely (one hour post injection) and chronically (three days after) (35). Delta-9-THC, 16 mg/kg, enhanced the stimulant effect of amphetamine, 4 mg/kg, but was found to protect some subjects from a toxic methamphetamine dose.

In an in vitro study (26), Delta-8 and Delta-9-THC have been found to cause some inhibition of the metabolism of aminopyrine and ethylmorphine in rat liver homogenates. This was not found in vivo.

9. Neurophysiological Effects

Cannabis has long been suspected of having tranquilizing properties. In evaluating this potential, Salustiano, et al (61) used chlorpromazine as a standard of comparison for cannabis extract. Cannabis extract was found to be twice as active as chlorpromazine in decreasing isolation-induced aggressive behavior in mice, but was much less efficient in protecting the mice from d-amphetamine toxicity.

Sampaio (62) has observed that extract of cannabis, THC and synhexyl abolishes the linguomandibular reflex in the dog even after atropine administration. Chlopromazine produces the same effects in a comparable dose range and the effect is abolished by administration of strychnine. In search of the mechanism of this action, the same group (47) found that THC depresses the presynaptic potential in the trigeminal

nerve, while the tibialis nerve was unaffected, suggesting a specific central depressant action. Others, using the synthetic analogue dimethylheptyl and neurophysiologic methods (16) have also observed this depression in cats and localized the effect to the forebrain area, as facilitation of the linguomandibular reflex resulting from forebrain stimulation was also depressed. They also found that dimethylheptyl occasionally depressed the monosynaptic myotatic reflex and depressed lower motor neurons, thus resembling the effects of thiopental, only more inconsistently. Boyd and Meritt have also observed that 0.2 mg/kg dimethylheptyl is equivalent to 2 mg/kg thiopental in raising the threshold for both EEG and behavioral arousal by action on the ascending reticular formation (17).

In animals, the cannabinoids produce definite changes in the electroencephalograms (EEG) after acute and chronic administration. However, dosage levels used in animal studies are usually higher than those administered in humans.

Bose (14) found that 15-30 mg/kg, i.p., of cannabis extract initially increased frequency in the rabbit's frontal cortex indicating stimulation while the parietal area was depressed; one hour after administration, both areas were depressed. Recovery was characterized by appearance of sharp waves and gradually increasing voltage suggesting increased excitability of neurons. Lipparini, et al (48) showed that, in animals with chronically implanted electrodes, 0.5-1 mg/kg IV Delta-8 or Delta-9-THC will abolish theta waves in the rabbit hippocampus, flatten the EEG

and give rise to traces of high voltage spike and waves. However, increasing the dose to 10 mg/kg did not produce grand mal EEG tracings but only increased stupor. Racemic Delta-8-THC (less than 6 mg/kg) produced no EEG or behavioral changes or corneal anesthesia.

Bicher and Mechoulam (8) also found changed cortical activity as evidenced by strong beta rhythm in the electrocorticogram (ECoG) in rabbits following Delta-8 or Delta-9-THC (8 mg/kg IV) treatment. The cortical arousal threshold was lowered and the length of ECoG arousal prolonged, suggesting midbrain excitation as well. Thus, morphine action, which produces a decrease in frequency in EEG and an elevated threshold of arousal response, can be differentiated from cannabis.

Similar effects were also reported by Boyd and Merritt (17) for the dimethylheptyl synthetic derivative. Studies with cats (6 mg/kg of Delta-9-THC i.p) produced only moderate synchronization of the EEG, which was easily interrupted by external stimuli.

In doses greater than 5 mg/kg, IV, Lipparini, et al (48) showed corneal arreflexia, marked motor deficit, synchronization of EEG and insensitivity to external stimuli after l-cannabidiol. This is surprising as cannabidiol had previously been reported as being physiologically and pharmacologically inactive. Its effects, however, differ from those of Delta-8 and Delta-9-THC in that spike and wave EEG pattern and diminution of voltage are not seen. These authors suggest that flattening of EEG tracings, disappearance of hippocampal theta waves, and spike and wave configuration of the EEG could replace corneal

arreflexia as a specific bioassay of THC activity. They also suggest that synthetic derivatives of Delta-8-THC such as the methyl and dimethyl,which are 5-10 times more potent than Delta-8-THC and show the same spectrum of activity in rabbits and cats as Delta-8 and Delta-9-THC, will have cannabis activity in man.

Barratt, et al (4) have noticed, in preliminary experiments, EEG changes in cats treated chronically (i.p. 16 mg/kg/day) or by inhalation with a marihuana extract. After 10-12 days, slow waves with spiking appeared in baseline recordings. Treatment was continued for a total of 23 days and the abnormal baseline persisted 22 days following end of drug administration. At lower doses (2 mg/kg) abnormal EEG tracings did not appear until the 25th day. Behaviorally, these cats eventually became less playful and withdrawn; normal behavior returned 3 days following the end of treatment. Seizures of any nature were not apparent. Chronic, high dose administration of Delta-9-THC has been found to reduce paradoxical sleep in rats.

Fenimore, et al (29), using autoradiography methods with tritium labeled Delta-9-THC, showed distribution of Delta-9-THC in various cortical and subcortical structures of the monkey brain. Relatively high accumulations were found in the lateral geniculate nuclei at a time when the animal would appear to be hallucinating. Similarly high concentrations were discovered in the amygdala, hippocampus, inferior and superior colliculi at the time of behavioral effects and marked

amounts in the cerebellum corresponded well with the monkey's motor incoordination. It thus appears that behavioral effects may be related to increasing concentration of cannabinoids in specific brain areas.

10. Behavioral Effects

The effects of cannabis are behaviorally both dose and species related but setting can also be a factor. Barry and Kubena (5) have demonstrated that rats show increase and/or decrease of spontaneous activity following Delta-9-THC, given intraperitoneally. They found that low doses (4 mg/kg) produced initial excitation followed by depression; the excitation could be exacerbated by using laboratory naive and nonacclimated rats and could be abolished by a higher dose (16 mg/kg). Rats' behavior with Delta-8 or Delta-9-THC has also been studied by Grunfeld and Edery (39). Following a 20 mg/kg i.p. injection with these compounds, rats have been observed to be ataxic, cateleptoid and flaccid. This dose disrupts learned behavior but reactions to unconditioned stimuli remain intact. Vieira, et al (68) have suppressed a conditioned avoidance response in mice and rats with 125 mg/kg, i.p. extract. Mice show a similar response accompanied by partial ptosis and piloerection. Irwin (45) found mydriasis in racemic Delta-8-THC treated mice and miosis after Delta-9-THC in the same species. The minimal oral dose for behavioral effects with Delta-8-THC in mice and cats was low (0.1 mg/kg) and peak effect was 2 hr. post-administration. Mice also exhibit decreased performance in the rotating rod test when given 10 mg Delta-9-THC, i.p.; no effect, however, could be elicited following subcutaneous injection.

The effects on social behavior in animals were studied by Carlini, et al (22). They found that chronic administration of cannabis extract, 10 mg/kg, i.p., could evoke fighting behavior in rats only with starvation as part of the regimen. On the other hand, a single dose of cannabis extract (10 mg/kg) has been shown by Santos (63) to decrease aggression in mice by 80% while motor activity remained unchanged; this response was demonstrated for fighter and non-fighter mice and the effect lasted nearly 7 hours. This decrease in aggressiveness has been compared by Garattini (33) to the effects of chlordiazepoxide. Siegel and Poole (65) have confirmed this effect and also noticed less group aggregation and temporary disruption of social hierarchies in a mice community.

Synhexyl (15 mg/kg, i.p.) in operant behavior tests, has been shown to increase curiosity in the rat by Abel and Schiff (2) and also to decrease food, but not water consumption. They also showed disruption of the suppressive effect in a conditioned emotional response situation (1).

Carlini and Kramer (21) observed improved maze performance by rats given 10 mg/kg, i.p., cannabis extract prior to testing. However, post-trial administration produced no effect or disruption of activity, thus distinguishing cannabis from other CNS stimulants (strychnine or picrotoxin) which improve maze performance when given pre or post-trial. Higher doses of cannabis were explored but, at these doses, motor activity was impaired.

Boyd, et al (15) also studied the effects of synthetic tetrahydrocannabinols (DMHP) in the rat in various operant behavior tests using positive food reinforcers at various dose levels. These compounds were found to depress all measures of behavior except on a mixed schedule, where they appeared to increase the ability of the animal to judge elapsed time; general performance on fixed ratio schedules was found more sensitive to these drugs than on fixed intervals. The overall effects were similar to that of pentobarbital. Scheckel, et al (64) report that monkeys receiving racemic Delta-9-THC (32 or 64 mg/kg, i.p.) exhibit initial excitation, including fine hand tremors, panic like states, hallucinatory activity and unusual limb positions. These signs lasted three hours and were followed by depression; nine subjects died after the high dose treatment. This study also revealed that racemic Delta-9-THC (4 or 8 mg/kg) reduced response rate by 50% in a continuous avoidance schedule, whereas 16-64 mg/kg increased responding 200%. Effects of the Delta-8 were different from those of the Delta-9. Delta-8-THC increased lever responding in the lower doses (2, 4 and 8 mg/kg) but the higher doses did not cause the depression or death seen with Delta-9. The monkeys also seemed to lack ability or motivation to perform complex tasks. Francois, et al (31) have confirmed this behavioral spectrum in monkeys and also report consistent vomiting after 8 mg/kg i.p. of Marihuana Extract Distillate (MED). The social dominance hierarchywas not changed by the drug, but expressions of dominance were changed, that is, the monkeys were less aggressive.

The general behavior of dogs is not unlike that of other animals previously studied, but excessive salivation, retching, vomiting and overt ataxia seem specific for dogs. This typical ataxia has since been used for a bioassay of cannabis action as well as the corneal arreflexia in rabbits (36).

In pigeons, Frankenheim, et al (32) found that both Delta-9- (0.3-3.0 mg/kg) and Delta-8-THC (3-10 mg/kg) given intramuscularly caused a dose dependent decrease in the rate of key pecking in a multiple operant behavior schedule. The Delta-9 isomer was found to be more than twice as potent as Delta-8-THC and tolerance was found after seven days of chronic administration.

11. Teratology

One of the pertinent questions regarding marihuana use in the population concerns the effects of repeated usage during pregnancy.

The experimental evidence reported so far has been contradictory. Once more, results seem to vary with species, mode of administration and doses used.

Miras (54) found that rats impregnated after being fed a diet containing 0.2% marihuana extract for several months showed a reduced fertility but the offspring produced were normal. In another study, pregnant mice injected intraperitoneally (i.p.) with 16 mg/kg of Cannabis resin on day six of gestation produced offspring which were stunted but not malformed. The same dose given on days 1-6 caused complete fetal resorption (57). In a second experiment using rats, the injection of 4.2 mg/kg of cannabis extract on days 1-6 resulted in a high frequency of malformed progeny (58). Congenital mal-

formations and abnormal fluid accumulations were also observed in fetal hamsters and rabbits after prenatal administration of large, multiple doses of marihuana resin (100-500 mg/kg), the teratogenicity being influenced by plant origin and seasonal variations (37, 38).

However, Borgen, et al (10) administering the pure Delta-9-THC subcutaneously to female rats in doses of 0.01 to 200 mg/kg as a solution in olive oil from day 1-20 of gestation did not find congenital abnormalities or stunting of offspring. However, average litter size was reduced by doses of 100 and 200 mg/kg. At doses of 10 mg/kg and above, maternal weight gain during pregnancy was diminished and length of gestation was increased by 1-2 days. Doses above 25 mg/kg caused a marked postnatal mortality of pups apparently due to inadequate maternal lactation. Females sacrificed on day 21 after 100 and 200 mg/kg dosages showed increases in the size of the adrenals, thyroid, and heart, while the mass of the liver was reduced. Thus, in contrast to published research with marihuana extracts, Delta-9-THC does not appear to be teratogenic in rats in doses up to 200 mg/kg given throughout gestation. The major effects noted were on the female rather than the progeny, and these appeared only with higher dosages.

This lack of teratogenic effect cannot be the result of a lack of penetration of Delta-9-THC through the placental barrier as Idampaan-Heikkila et al (44) found that 15 minutes post i.p. administration, Delta-9-THC-H^3 crossed the placenta and peak concentration were

achieved 30 minutes after administration in the hamster. Fetuses from animals injected early in pregnancy contained nearly three times more radioactivity than fetuses from animals injected at a later time in pregnancy; this difference was even more apparent after subcutaneous administration. The placenta was shown to contain more radioactive label than the fetus by either route and the fetus contained more label than maternal plasma or brain.

A few investigators have studied the cytogenic effects of marihuana and so far no observable chromosomal changes have been found (55, 51).

12. Metabolism

With the availability of Tritium and Carbon-14 radioactive labeled Delta-8 and Delta-9-THCs last year, major advances in the study of the metabolism of these compounds took place. These studies showed that the cannabinoids disappear rapidly from the blood and metabolism occurs mostly through the liver of the species studied: mice, rats and rabbits. So far, metabolism is mainly an hydroxylation process (3, 7, 18, 30, 56, 67, 69) and the 11-hydroxy metabolites of Delta-8 and Delta-9-THC have been reported to have the same pharmacologic profiles as the parent compounds (67, 69). Distribution studies after intravenous administration and inhalation have shown relatively high concentration of radioactivity in the lungs (3, 42). Excretion is mostly through the feces. Even after single dose administration, radioactivity can be found in the feces for days after administration. So far, only two metabolites have been characterized (the mono and

dihydroxy derivatives) but a significant number of uncharacterized metabolites have been reported by the various researchers (3, 69). Preliminary experiments indicate that the primary metabolite may vary with the species, which would explain species differences in terms of response to cannabis effects.

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EFFECTS IN MAN OF SHORT AND LONG-TERM USE OF CANNABIS SATIVA

Therapeutic Uses of Cannabis

Acute Effects: Experimental Findings

Chronic Effects: Experimental Findings

Health Consequences for the Individual of Marihuana Use

EFFECTS IN MAN OF SHORT AND LONG-TERM USE OF CANNABIS SATIVA

Cannabis sativa is one of man's oldest and most widely used drugs. It has been consumed in various ways as long as medical history has been recorded and is currently used throughout the world by hundreds of millions. (2,3,81,101,211) A fairly consistent picture of its short-term effects is presented in the many publications on Cannabis users. There are, however, strongly contradictory opinions about whether the ultimate effects are harmful, harmless or beneficial to human functioning. (166) Despite these conflicting opinions, from the scientific point of view, the literature is as clear, if not clearer, than for many other botanical substances consumed by man. Most of the older reports suffer from multiple scientific defects such as biased sampling, lack of control groups and use of substances of unknown potency. However, contrary to popular belief, much is known about the use of Cannabis by man. (67)

Therapeutic Uses of Cannabis

There is no currently accepted medical use of Cannabis in the United States outside of an experimental context. However, there was a time when extracts of Cannabis were as commonly used for medicinal purposes as aspirin today. (127,196)

Medical use of Cannabis is mentioned as early as 2737 B.C. when it was recommended in China for female weakness, beriberi, constipation, absent-mindedness and surgical anesthesia. It was used medically in India before 1000 B.C.. After 500 A.D., Cannabis spread westward to Assyria, Persia and other Arabian lands, where it was used medically as a balm and an antiseptic. Cannabis was probably re-introduced to Europe by Napoleon's

soldiers returning from Egypt, although it had been used during the Middle Ages to treat burns, earaches, ulcers and uterine disease. (127,149,159, 196,211)

There was only minor mention of Cannabis' psychoactive effects in ancient China although soon after its introduction in India, it became an integral part of the Hindu culture as a mind altering aid to meditation.

A British physician serving in India, W. B. O'Shaughnessy, reintroduced Cannabis into Western medicine. In 1839 he reviewed the literature of its use in Indian medicine during the preceding 900 years, and he described his experiences with the drug in the treatment of seizures, rheumatism, tetanus and rabies. He found it an effective analgesic, anticonvulsant, muscle relaxant and sedative in man. Later in the 19th century its use in medicine spread rapidly. Numerous reports in the literature described its therapeutic effectiveness over an extensive range of ailments, including: gynecological disorders such as excessive menstrual cramps and bleeding (23,190), treatment and prophylaxis of migraine headaches (12,70, 176), alleviation of withdrawal symptoms of opium and chloral hydrate addiction (13, 132), tetanus (73,150,158, 160), insomnia (132), delirium tremens (176), muscle spasms (176), strychnine poisoning (88), asthma (59, 157), chorea (157), dysentery (68), labor pain (48, 123), psychosis, spasmatic cough, excess anxiety, gastrointestinal cramps, depression, nervous tremors, bladder irritation, and psychosomatic illness. (196)

However, the use of Cannabis preparations gradually disappeared from medical therapeutics at the end of the 19th century for the following reasons: unavailability of injectible preparations, difficulty in obtaining standard potency batches, wide variability of individual responses to

the same dose. Also important was the introduction of a wide variety of synthetic drugs which were easier to produce and more efficient to administer although not always as effective and usually more toxic than Cannabis. Nevertheless, there were 28 pharmaceutical preparations containing Cannabis in use when passage of the Marijuana Tax Act in 1937 effectively banned Cannabis as a medicine as well as an intoxicant. (185,196)

In 1947, experiments revealed that natural tetrahydrocannabinol and a synthetic derivative, synhexyl, were effective anti-convulsants. (123) In 1949, THC was demonstrated to be effective in the control of seizures in several epileptic children who were unmanageable with the conventional drugs. THC was reported to have a synergistic effect with diphenylhydantoin and phenobarbital. (48)

Recently, marihuana or its synthetic analogues have been experimentally considered for the treatment of the withdrawal of the chronic alcoholic (203), and as a substitute for alcohol in chronic alcoholism therapy. (147) Extracts of unripe Cannabis have also been demonstrated to have antibiotic activity against certain bacteria and fungi. (66,109,173) Other THC analogues may prove to be valuable agents for the treatment of high blood pressure and uncontrollable fevers. (191)

Some preliminary studies have suggested that an oral extract of marihuana may be a useful agent for the management of terminal cancer patients. The beneficial effects of marihuana demonstrated over a short period of time were stimulation of appetite, euphoria, increased sense of well-being, mild analgesia and an indifference to pain which reduced the need for opiates. (199)

Thus, Cannabis has had widespread usage in medical therapeutics for about 5000 years. In the future, Cannabis or its synthetic analogues may prove to be valuable therapeutic agent. (149,196)

Acute Effects: Experimental Findings

It is important to recognize that the response to Cannabis varies according to the form in which it is consumed, the dose and the route of administration (typically by smoking or eating in humans). Also, the non-drug factors of set and setting must be considered in evaluating the results of those laboratory studies. In the following discussion dosages are expressed in terms of the Delta-9-THC content (the major psychoactive ingredient). Since it is only recently that laboratory reports routinely cite the percentage of THC, for older reports the estimated THC equivalent is based on the assumption that the average THC content is on the order of 1% for marihuana, 3% for Indian ganja and 5% for hashish. Although given samples may vary widely in actual THC content such a very rough measure is useful as the basis for comparisons between various experiments and observations. Actual THC content varies greatly depending on such variables as the parts of the plant included in the mixture, genetic origin and mode of cultivation. (Cf. Section III, The Material)

Dose and Route of Administration

Four studies have described the effects of administering pure Delta-9-THC (the major psychoactive ingredient in marihuana) to humans at oral doses of 5-70 mg. and smoked doses of 2-20 mg. Isbell, et al. (105,106), reported that smoked material was nearly three times as effective as orally consumed material in producing equivalent peak pulse rate increases and

subjective effects. His subjects, former opiate addict patients and experienced marihuana smokers, readily identified the marihuana-like effect of THC. Threshold doses of 2 mg. smoked and 5 mg. orally produced mild euphoria; 7 mg. smoked and 17 mg. orally, some perceptual and time sense changes occurred; and at 15 mg. smoked and 25 mg. orally, subjects reported marked changes in body image, perceptual distortions, delusions and hallucinations. Waskow, et al., (213), administered 20 mg. Delta-9-THC orally to "marihuana naive" prisoners. A slight euphoria, mildly unpleasant somatic effects and a few marked mental changes were noted. Hollister, et al., (98), elucidated the characteristic clinical syndrome of euphoria followed by sedation and sleep with marked psychic changes following oral administration of Delta-9-THC in doses of 30-70 mg., (median 50 mg.), to students experienced with marihuana. Dornbush, et al., (156), demonstrated great variability among moderately experienced users in the dose range required to produce behavioral effects (anywhere from 5-20 mg. Delta-9-THC). 5 and 10 mg. doses were inadequate; 15 and 20 mg. doses produced variable changes. A 20 mg. dose administered in the fasting state produced "intense" changes, indicating the importance of gastro-intestinal absorption when the drug is taken orally.

Other experiments on humans have utilized either smoked marihuana or an oral extract of marihuana. The most extensive study was conducted by Mayor LaGuardia's Committee on Marihuana. (134) Both marihuana users and non-users were tested with an oral marihuana extract (dose range 30-50 mg. THC and a few 330 mg. THC) with characteristic euphoria and clinical syndrome resulting at lower doses but with dysphoria at higher doses.

Subjects who smoked were instructed to do so until they felt "high." A characteristic euphoria and clinical syndrome was produced, especially among the user group, at doses of 8-28 mg. THC.

Weil, et al., (218), found smoked marihuana (18 mg. THC) resulted in a relatively high level of intoxication among experienced users, but lesser subjective effects were reported by naive subjects. Meyer, et al., (144), reported that a 3.1-3.8 mg. THC dose of smoked marihuana produced the usual social high in casual and heavy users who were permitted to smoke as much as they chose. Clark, et al., (39, 40), reported on the behavioral effect of approximately 20, 30 and 45 mg. THC contained in an alcohol extract of marihuana. His marihuana-naive subjects experienced few behavioral effects at the lower two dose levels, but the 45 mg. dose produced the characteristic effects. However, experienced users studie by Jones, et al., (108), were able to detect the characteristic effects of an oral extract of marihuana at dosages as low as 4.5 mg. THC. Jones was impressed by the quantity and quality of the different subjective effects produced by the oral and smoked preparations. Interpretation of marihuana smoking may be complicated by the placebo effect. That is, an individual smoking an inert material similar in taste and odor to Cannabis may subjectively believe he is "high" although the material itself is without physiological effect.

Forney and Manno (127, 128) using a specially constructed smoking machine have estimated that only 50% of the Delta-9-THC present in a marihuana cigarette is delivered unchanged to the smoker's lungs. There was very little change from Delta-9 to Delta-8-THC in the smoking process. The percentage of delivery did not change by varying inspiratory volume or the duration of each inhalation. Studies by Foltz, et al., (69), confirmed

that 50% of the Delta-9-THC in a marihuana cigarette was destroyed (or lost) during the smoking process. No measurable conversion of Delta-9-THC to Delta-8-THC or vice versa was observed. There was 7% conversion to cannabinol and less than 2% to cannabidiol.

Similar time-action curves have been observed for pure Delta-9-THC and marihuana. (98,106,134) After smoking, symptoms began almost immediately and persisted for one hour at lower doses and 3-4 hours at higher doses. Symptom onset after oral administration requires from one half to one hour, reaches a peak in 2-3 hours, and persists for 3-5 hours for the lower doses and up to 8 hours or more for the larger doses.

In summary, the effective dose for experienced subjects is in the range of 2-20 mg. THC when adminstered by a single smoked dose. The comparable range for oral administration is 5-40 mg.. Oral administration of doses above 40 mg. THC produce dysphoria and unpleasant somatic symptoms in many subjects. Comparable smoking dose levels are uncommon and have not been investigated. Subjective responses of naive groups tend to be much more variable and unpredictable than those of experienced users.

Subjective Effects

There is much individual variation in the psychological effects produced by Cannabis. The widely divergent accounts to be found in published papers may be accounted for in part by ethnic and social differences in the populations studied, and in part by the effects of different preparations of the drug.

The psychological effects of acute intoxication were first described in detail by Moreau de Tours, and even after the passage of more than a century, it is difficult to improve on his clinical description. The

effects he mentions include euphoria, excitement, disturbed associations, changes in the perception of time and space, heightened auditory sensitivity, fixed ideas, rapidly changing emotions, and illusions and hallucinations. (175)

In Westerners, though the order of events may vary a great deal, a typical sequence is euphoria with restlessness; then confusion, disturbed visual and auditory perception; then a dreamy state; and finally depression and sleep. On waking after sleep, there may be numbness, dysarthria, and some amnesia. Subjects drawn from Near Eastern populations,in contrast, may become gay or relaxed though it is not rare for anger to be expressed in some act of violence. Noisy laughter may be accompanied by feelings of sadness. (175)

Tart (202) discusses common experiences of marihuana intoxication as related by users. Sensory perception is often subjectively improved, both in intensity and scope. Visual imagery is often quite vivid but under subjective control. The individual feels less concern with controlling his activities. Distortion of time sense and space perception are common. Common emotional effects are euphoria, relaxation, disinhibition and feelings of well-being. Commonly experienced cognitive effects at the time of use are a dulling of attention, fragmentation of thought, impaired immediate memory, altered sense of identity, increased suggestibility and a feeling of enhanced insight. Other less common effects are dizziness, a feeling of lightness, ataxia, nausea, hunger, paresthesias and exaggerated laughter. Mild psychotomimetic phenomena are experienced in a wave-like fashion with larger doses (greater than typical social usage). These include distortion

of body image, depersonalization, visual distortions, synesthesia, dream-like fantasies and paranoid reactions. Marked anxiety and panic may accompany these phenomena. Occasionally this may occur at relatively low doses with naive individuals. The anxiety and panic is usually alleviated if supportive friends are present. However, nearly all the common effects seem either emotionally pleasing or cognitively interesting and, therefore, highly desirable to many users.

Physiological Effects

The most consistent physiological sign is an increase in pulse rate. This change is sufficiently dose-related and reproducible for use as a quantitative assay with both oral and smoked pure THC. (106,144) Smoked doses of 4 and 15 mg. Delta-9-THC have resulted in average pulse rate increases of 22 and 34, respectively; oral doses of 8 and 34 mg. produced increases of 18 and 33, respectively. Correlation between dose and pulse increase is not especially high across investigators, but all report increases of 10-40 beats for doses ranging from 2-70 mg. THC. (42,55,98, 127,128,134,213,218) This occurs regardless of prior experience with marihuana. Two studies using doses up to 70 mg. Delta-9-THC, and an extract containing 255 mg. THC produced little or no electrocardiographic abnormalities (105,134), or change in circulation rate.

Conjunctival injection (i.e. reddening of the eyes) is another highly consistent physical sign of intoxication. (5,6,98,105,128,213,218) This finding has been detected with smoked doses as low as 2.5 mg. THC. (127) Weil (218) found such reddening in all of his chronic marihuana users and in 8 out of 9 naive subjects using a 18 mg. THC dose. Swelling of the

eyelids (6), ptosis (106), photophobia and nystagmus (5) have also been reported in some individuals. Enlargement of the pupils and a sluggish reaction to light were reported in earlier studies. (133,134) However, recent experiments in which pupil diameter was systematically measured revealed no dilation at doses up to 70 mg. THC. (55,98,105,218) In fact, Hepler, et al. (89) using sophisticated instrumentation demonstrated a slight but consistent pupillary constriction present within 5 minutes of smoking, a preservation of normal light responsiveness and a depression of pupillary responsiveness to near stimulation appearing in a few hours, probably representing fatigue and sleepiness. Frank, et al. (19,72) demonstrated a marked and consistent increase in glare recovery time which persisted for several hours and was not dose related. Further tests revealed that this finding was not related to change in illumination threshold or pupil size. This may indicate a significant hazard in night driving. Studies on near and far visual acuity, eye muscle balance, visual field acuity, depth and color perception are incomplete. Caldwell, et al. (24,25,26)have demonstrated neither an impairment nor an improvement in objective visual acuity or in the perception of light brightness in naive and experienced users at 4-6 mg. smoked THC doses. Clark, et al. (39) demonstrated no effect on depth perception, duration of after image or visual motor coordination tests.

Reports on the effects of a wide range of marihuana dosages on blood pressure are inconsistent. Investigators using pure THC have reported slightly lowered blood pressure. (98,105,213) Others have reported small increases. (55,134) Some have been unable to demonstrate any change using smoked or oral preparations. (199)

Body temperature is generally unchanged. (98,106,199) Little or no effect on respiratory rates, (55,105,218), lung vital capacity or basal metabolic rate is noted. This is true over a wide dosage range. (134) Dryness or the mouth and throat are uniformly reported. (6) Increased frequency of urination is often reported, but increased urine volume has not been consistently recorded. (6,134) Another carefully controlled clinical investigation (199) revealed no changes following oral ingestion of a marihuana extract in such measures of kidney function as: routine urinalysis, fluid intake, and 24 hour urinary output, electrolytes, protein and creatinine. Eight subjects and dosages ranging from 7.5 mg. to 52.5 mg. were studied. Hollister (98) also demonstrated no change in normal 24 hour creatinine excretion. The LaGuardia Commission also found no change in kidney function. (134)

Biochemical Effects

Reports of increased hunger (5,6,127,134) especially for sweets during Cannabis intoxication have focused attention on possible changes in blood sugar level. Early investigators reported decreases (12,121), but more recent studies have found no change (56,92,98,105,127,199,218) or a slight increase (128,134) or both. (153) Hollister, et al. (92) found an increase in total food intake which was significant after 26 mg. THC when the subject had eaten breakfast but not when he was in the fasting state. Reports of appetite stimulation and subjective hunger occurred in slightly more than half of the subjects. Hollister was unable to demonstrate a change in blood sugar. Free fatty acid levels were unchanged while a decrease was observed in the placebo control group.

Hollister (93,98) analyzed blood and urine samples subsequent to oral administration of either THC (15-70 mg.) or synhexyl (50-150 mg.). Total white blood cells increased and absolute eosinophils decreased. No significant changes were demonstrated in platelet serotonin content, plasma cortisol level or urinary catecholamine excretion. These findings indicate a lack of major effects of marihuana on the above physiological measures of stress. This differs significantly from findings in schizophrenics and individuals treated with LSD or mescaline who show such stress reactions. The hypothesis has been advanced that in most individuals the profound euphoriant and sedative effect of marihuana may serve to prevent the stress of the psychotomimetic experience that results with high dosages of THC.

Two studies (134,199) have examined possible oral marihuana induced hematological and blood chemistry changes. No changes were found in: red blood cell structure or number; differential and total white blood count; platelet count; reticulocyte count; blood urea nitrogen; concentration of serum sodium, potassium, chloride, bicarbonate, calcium, phosphorous; liver function tests (alkaline phosphatase, bilirubin, SGOT); protein electrophoresis; uric acid concentration. Doses ranged from 7.5 mg. to 75 mg. THC equivalent.

Neurological Effects

Neurological examinations have consistently revealed no major abnormalities (134,180,199) during marihuana intoxication. Muscle strength and performance of simple motor tasks are, however, affected. Several investigators (65,98,134) noted decreased leg, hand and finger strength at oral

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dosages of 50 to 75 mg. THC. However, electromyography has been reported to be within normal limits even at up to 52.5 mg. THC taken orally. (199) Most investigators (98,105) have not demonstrated change in threshold for elicitation of deep tendon reflexes although Rodin (180) described a slightly increased briskness in the knee jerk. Fine hand tremors are often reported. (6,12,40,134) Decrements in hand steadiness and static body equilibrium appear to be dose-related phenomena (127,134) although other investigators have been unable to demonstrate these (180,199). Other cerebellar dysfunctions are not evident. Cranial nerve function and somatic sensation were unimpaired. (180)

Cannabis users often report increased auditory sensitivity and esthetic appreciation of music. Objective tests of auditory acuity including pitch, frequency and intensity or threshold discrimination have been found to be unchanged. (4,24,25,26,39,134) However, two earlier investigators (211, 223) reported definite objective improvement in auditory acuity in several of their subjects.

Improvement in visual acuity is often reported by users of marihuana. However, investigators have been unable to demonstrate significant changes in objective visual acuity, brightness discrimination (24,25,26) or visual flicker fusion frequency discrimination. (39) Depth perception, estimating length of lines (39,134) and field independence measured by the rod-and-frame test are all unchanged. (94,108)

Rodin (180) has demonstrated a slight but statistically significant improvement in vibratory sense. Both Rodin and Williams, et al. (223) found other sensory discriminations including touch and two point discrimination unchanged. However, one investigator, Rumpf, reported an impairment

in two-point discrimination. (211) Pain sensitivity has been shown to be decreased (199) as is also suggested by marihuana's early medical use as an analgesic. No change has been demonstrated in olfactory threshold or in taste discrimination. (223)

One of the most frequently reported effects of intoxication is a distortion of the sense of time. Time is almost always overestimated, that is, perceived as being longer than clock time. This phenomenon has been experimentally confirmed by most investigators, (6,40,56,94,218,223), and is much greater for filled as opposed to unfilled time, i.e., when the subject estimates the elapsed time while performing a task. This overestimation is found for time periods ranging from seconds to hours. Overestimation error appears to increase with longer time periods. (40) Hollister found that the overestimation of time produced by marihuana intoxication was much closer to clock time than the gross underestimation induced by alcohol or dextroamphetamine ingestion. (94)

Reported changes in resting electroencephalogram (EEG) during single dose administration have generally been minimal, inconsistent and within normal limits with rare exceptions. Early investigators generally recorded an increased abundance of low voltage fast activity and a slight decrease in alpha wave percentage and frequency. (222,223) This has been reported recently in several subjects by Jones. (108) Recently, several investigators have shown no statistically significant alteration of normal EEG with only minor variation between subjects at doses of THC up to 52.5 mg. orally. (6,199,108) Rodin (180) has detected a slight but statistically significant shift toward the slower alpha frequencies (9 to 10 cycles per sec) in 10 experienced marihuana users who smoked to achieve their usual

"social high."The average dose of THC consumed was 10-12 mg.. Hollister confirmed this finding of increased and more synchronized alpha rhythm using 32 mg. THC orally in 16 subjects. (99) There was no change in peak or mean frequency or total waves noted. This minimal EEG change resembled drowsiness or sleepiness and was not readily distinguishable on visual inspection from the placebo control EEG when drowsiness also occurred. Preliminary studies by Rickels appear to support these findings. (177) In addition, Rodin (180) has reported no significant change in cerebral evoked potentials at 15 different sites for light, sound and passive joint movement. He also found no significant change in photic driving response. Jones (108) described a decrease in visual evoked response in preliminary work. Thus far, EEG findings following acute administrations at levels of social usage do not suggest changes in brain functioning indicative of gross cerebral dysfunction. Adult EEG wave changes are considered significant clinically only at frequencies less than 8 cycles per second. This occurs characteristically in certain toxic and degenerative central nervous system processes.

Preliminary work on the effect of marihuana on sleep has demonstrated an increase in total Rapid Eye Movement (REM) sleep time. (177) (This is the deep period of sleep when dreaming occurs.) Rickels (178) has also done preliminary work on evoked palmar skin resistance and evoked heart rate responses during marihuana intoxication. The former was greater and more variable and subjects demonstrated delayed habituation to it.

Psychomotor and Cognitive Effects

Intoxication with psychoactive substances affect psychomotor and

cognitive functions. That marihuana is no exception is apparent from the assertions of users. Experimental confirmation is evident from a wide range of studies. (39,40,42,56,94,108,127,128,134,136,141,142,144,186, 217,218)

In general, above a threshold dose of 15-30 mg. orally or 4-10 mg. smoked, a performance decrement or impairment on a wide range of tests occurs. In many instances, the degree of impairment is dose related and varies during the period of intoxication. A minimal decrement is observed, both subjectively and objectively, at lower dosages and during the time period when the level of intoxication is increasing or declining. A moderate impairment occurs at higher dosages and during the period of peak intoxication.

Naive subjects do not react the same as do experienced marihuana users at the same dose levels. Naive subjects commonly report less marked subjective effects than those reported by experienced users. However, naive subjects demonstrate greater decrement in actual performance. (218) Experienced users seem better able to compensate for the acute drug effects on ordinary kinds of performance, at least at lower dose levels. (39,40,42, 108,144,217)

The complexity of the task is related to performance while intoxicated. Simple and familiar tasks are minimally affected. But, if the task is complicated enough, decrements in performance are demonstrable. (217) In addition, the effects of marihuana are not consistent from subject to subject with marked individual differences in performance. (39,40,127)

The intensity of the intoxication and the degree of related performance deficit varies cyclically from moment to moment. This contributes to the considerable variability in performance between subjects and in the same subject at different times. (40, 141)

In summary, marihuana in acute administration appears to act as a mild mental intoxicant in a neutral laboratory setting. (108,218) At the level of intoxication characteristic of the "normal social high," it produces a subtle alteration in emotional state characterized by a feeling of euphoria, excess jocularity, and a minimal but subtle impairment of higher intellectual functioning. (180) In most instances, this alteration in mental functioning is not consistently recognizable by an observer who does not know the user has received the active drug. Typically no gross unusual behavior, inability to function or intellectual performance is apparent. When subjects concentrate on the task being performed, no objective evidence of intoxication may be apparent. The subjects are easily able to "suppress the marihuana high" at least on the simpler, more familiar tasks. (180)

Marihuana users consistently report interference with short-term and immediate memory functions. (202) Researchers have therefore focused experimental investigation on these areas. Very simple memory tasks (forward and backward digit span) have given mixed results. (134,141,213) More complex tasks in which memory and mental manipulations are required show larger dose related impairment. (108,134,141,213) This is exemplified by simple cognitive functions performed while distracted by delayed auditory, feedback or background noise. (127) More complex cognitive functions such as learning of a digit code (40), digit-symbol substitution (218), reading comprehension (40), speech (217) and goal directed arithmetic tasks (141) are all impaired.

Clark (40) suggests that marihuana affects the mental processes involved in recent memory and types of decision requiring recent memory

and sustained alertness. Weil (218) describes subtle difficulties with speech experienced by marihuana smokers. The primary difficulty found was in "remembering from moment to moment the logical thread" of the conversation. He hypothesizes that more effort is necessary to retrieve information from the brain's immediate memory storage when high.

Melges, et al. (141) demonstrated that marihuana intoxication significantly impaired the ability to: (1) retain events from the preceding few seconds to minutes; (2) shift attention appropriately from one focus to another; and (3) to organize and coordinate serially in time recent information while pursuing a goal directed task. He termed the result of these inabilities "temporal disintegration," that is, difficulty in retaining, coordinating and indexing serially in time those memories, perceptions and expectations which are relevant to the goal being pursued. He theorizes that episodic impairment of immediate memory is the basic cause of these difficulties. He suggests that extraneous perceptions and thoughts occupy the void in thought created by the memory lapse, thus causing disorganized speech and thinking.

Melges (142) also suggests that "temporal disintegration" is associated with "depersonalization" during marihuana intoxication. He hypothesizes that impaired immediate memory leads to a "fragmentation and disorganization of temporal experience." This blurring of the personal past, present and future context in which the individual has his personal identity causes him to experience himself as strange and unreal (depersonalized) during marihuana intoxication. Melges feels the response to depersonalization is unique for individuals. When the distortion of self is recognized as time-limited and drug related, it is euphorogenic. But when an individual's

personality causes him to fear that loss of identity and control of self may not end, acute anxiety and panic reactions may arise.

Driver Performance

There are two preliminary studies of the effect of social marihuana intoxication on automobile driving performance. Crancer (42) studied the effect of smoked marihuana (22 to 66 mg THC) on simulated driving performance. The subjects were seated in a console model of a recent car and performed the usual driving maneuvers in response to a series of situations portrayed in a film. Experienced and naive subjects demonstrated no significant decrement in accelerator, brake, turn signal, steering and speed variables as compared to non-drug control subjects. Subjects intoxicated with alcohol to the legal intoxication level (100 mg % blood alcohol concentration) made significantly greater errors (15% more) than both the non-drug control and marihuana subjects. Intersubject variation was observed during marihuana intoxication. Thus, about one-half the subjects did better and one-half worse than the controls. The subjects indicated that they felt their driving performance was affected but that they could compensate by driving slowly and cautiously. It should, of course, be noted that the legal level of alcohol intoxication is probably higher than typical levels of social use of alcohol. By contrast the marihuana level used in this research may have more closely approximated a typical level of social marihuana use.

McGlothlin et al (136) believe laboratory measures of attention skills are one of the best predictors of actual driving performance. He has consistently demonstrated that oral or smoked marihuana (dose 15 mg THC) produces decrements in measures of vigilance, divided attention and psychological refractory time as does alcohol (peak blood alcohol concentration 68 mg %, in comparison to placebo controls). Perhaps this apparent

discrepancy can only be resolved in a more complex, sophisticated simulator which accurately reflects the complexities of actual driving.

Genetic Effects

Concern over the possible role of cannabis in causing birth defects is an inevitable consequence of our generally increased awareness of the teratogenic and mutagenic potential of drugs. Although there are two isolated case reports (28, 85) of birth defects in the offspring of parents who have used both cannabis and LSD it is impossible to attribute a causal role to the drugs. Because of these findings, Neu et al (154) have examined the effects of Delta-8 and Delta-9-THC added to human micro-blood cultures. This caused a drastic decrease in the rate of cellular division but did not cause structural damage.

Because of the basic importance of the question of birth defects associated with drug use, researchers are pursuing the inquiry. It should, however, be emphasized that there is little basis at present for suspecting that cannabis use is likely to lead to such defects. Nevertheless the use of any drug substance of unknown teratogenic or mutagenic properties is obviously unwise especially in women during the child bearing years.

Metabolism

One study has been published regarding the biological fate of Delta-9-THC in man. Lemberger et al (119) injected a tracer dose (0.6 mg) of radioactively labeled Delta-9-THC intravenously into three marihuana naive subjects and followed its course in blood, urine and feces. They found that Delta-9-THC is completely metabolized in man. The metabolites appear in the blood within ten minutes, 30% are excreted in the urine and 50% in the feces over a period of eight days. Most are excreted in the first

few days. Delta-9-THC in the plasma declines rapidly during the first hour after injection and more slowly thereafter. The initial rapid decline, occurring in the first few hours, probably represents metabolism and a redistribution of Delta-9-THC from the blood to the tissues (including brain). This is followed by a slow declining phase over the next three days which presumably represents retention and slow release from tissue stores. Negligible amounts of Delta-9-THC are excreted in the urine and faces. In the present study, the 11-hydroxy-Delta-9-THC metabolite appears to be only a minor metabolite of the Delta-9-THC and the remainder consists of unidentified more polar compounds. No data are presently available dealing with metabolic disposition of THC in experienced marihuana users.

Pharmacological Classification

The chemistry and clinical pharmacology of marihuana is distinct from that of the opiates, ethyl alcohol, barbiturates, amphetamines, atropine alkaloid-like drugs and psychotomimetic compounds (e.g., LSD, mescaline, psilocybin). However, the pharmacological action of marihuana has some similarities to properties of the stimulant, sedative, analgesic and psychotomimetic classes of drugs.

In large doses, cannabis drugs bear many similarities to the psychotomimetics. Isbell (104, 105) described marked distortion of auditory and visual perception, hallucinations and depersonalization. He found LSD was 160 times more potent as a psychotomimetic than Delta-9-THC. The wave-like experiencing of effects is also similar for both types of drugs. (40, 141). However, there are numerous differences between

cannabis and the strong hallucinogens: increased body temperature, blood pressure and constricted pupils do not occur with THC (19, 72, 89, 104, 105) or related synthetic analogues (19); sharply increased pulse rate and conjunctival reddening are common for cannabis but not for LSD (95) or mescaline (96); cannabis intoxication ends in sedation and sleep while wakefulness is characteristic of LSD and mescaline; acute changes in brain wave patterns characteristic of LSD are absent with marihuana (99, 108, 181); tolerance is not appreciable, at least at the usual doses for cannabis but occurs very rapidly with the psychotomimetics; there is no cross-tolerance in man between LSD and Delta-9-THC (104); the subjective effects of even large doses of marihuana are milder and more easily controlled than for LSD. The differing subjective effects of the two drugs are readily distinguished by users (104), and Delta-9-THC and marihuana even at high doses (70 mg) appear to lack the major effects on biochemical and clinical measures of stress found with the psychotomimetics (93, 95, 96).

In low doses, the effects of marihuana and alcohol are similar. Both produce an early excitant and later sedated phase, and are commonly used as euphoriants, relaxants and intoxicants. At low doses, subjects experience difficulty differentiating the effects of alcohol from marihuana and placebo. This difficulty is apparent especially when the marihuana and placebo are smoked and smell and taste senses are intact. But, this appears to diminish as the dosage is increased. The marihuana high is subjectively easily distinguishable from alcoholic intoxication. (92, 94, 108, 127)

The margin of safety for Delta-9-THC is far greater than that of ethyl alcohol (19). In large doses alcohol acts as a general anesthetic

producing a primary and continuous depression of the central nervous system. Experiments have shown that alcohol decreases mental and physical performance but does not alter sensory perceptions. It does slow brain wave rhythm. (179)

Hollister et al (94) compared the effects of 95% ethyl alcohol (50-60 gm dose) and marihuana extract (27-37 mg THC dose) on mood and mental function. He found alcohol and marihuana similar in their effects except for the alteration of perception that was produced by marihuana but not by alcohol. Both produced decreased activity, euphoria and sleepiness, and decreased performance on psychometric tests. Marihuana led to moderate overestimation of time while alcohol produced grossly exaggerated underestimation of time. Thus, the estimate of elapsed time during marihuana intoxication was more accurate than with alcohol. Hunger and food consumption were increased by marihuana and decreased by alcohol. Neither changed blood sugar level but alcohol decreased free fatty acid level. (92)

Manno et al (128) compared the effect of smoked marihuana (5-10 mg THC) with a subintoxicating level of alcohol (50 mg % blood alcohol concentration which is about the level produced by three bottles of beer in a 150 lb man) on performance on a pursuit rotor task and on mental function tests while distracted by delayed auditory feedback. This alcohol level was the threshold level to produce decrements in performance in a previous study with these tests. He concluded that performance decrement produced by marihuana was equivalent to that produced by alcohol. The combination of alcohol and marihuana generally led to a poorer performance than either drug alone.

In summary, marihuana cannot be accurately classified without specifying dose level. In small doses stimulation followed by sedation

occurs. In high doses, particularly with Delta-9-THC or concentrated oral extracts of marihuna, psychotomimetic effects are possible, but these are rarely attained (or sought by users) with smoked marihuana. Pharmacologically, cannabis is unique and distinct from the psychotomimetics, opiates, barbiturates, and amphetamines. Qualitatively, as an acute psychoactive agent, marihuana resembles alcohol but does not produce the same central nervous system and general physiological effects associated with alcohol.

Chronic Effects: Experimental Findings

Marihuana has been administered to human subjects for extended periods of time in only a few studies. Williams (223) reported in 1946 on the oral administration of synhexyl (a synthetic marihuana analogue) for 26 days and marihuana cigarettes for 39 days to prisoners who were experienced marihuana smokers. Subjects were permitted to consume the drugs freely any quantity they desired. The number of marihuana cigarettes (no estimate of the Delta-9-THC content available) used increased slightly over the 39 day period. The range was from 9 to 26 with a mean of 17 per day. The mean amount of synhexyl consumed by the second group of six subjects increased steadily from 200 mg the first day to 1600 mg daily at the 26th day. Abrupt discontinuation of synhexyl resulted in subjective reports beginning three days later of restlessness, poor sleep, reduced appetite, "hot flashes" and perspiration. One subject exhibited a brief hypomanic reaction and another developed a severe emotional reaction. However, there were no observable symptoms of abstinence following the abrupt termination of marihuana smoking. Thus, there was only minimal evidence of the possible development of physical dependence or tolerance to marihuana. Tolerance and physical dependence did appear to develop to oral synhexyl. Synhexyl acts differently (onset slower, duration longer) pharmacologically than Delta-9-THC (98) and probably is metabolized differently.

Measures taken during the drug period revealed:

Measure	Interval	Marihuana	Synhexyl
Rectal temp.	Daily	Increased slightly	Decreased slightly
Pulse rate	"	Increased for 3 weeks, then returned to normal	Increased initially, then decreased below normal
Respiratory Rate	"	No change	Decreased
Systolic blood pressure	"	Slightly increased	No change
Body weight	"	Increased	Increased
Caloric intake	"	Initial increase, then progressive decline	
Sleep	"	Increase	Increase
Mood	"	Euphoria for several days, then general lassitude & indifference	Euphoria for 3 days, then increased lethargy & general loss of interest
Coordination	"	No change	No change
Confusion	"	Mild	Mild
General intelligence tests	Baseline before medication 14 days on medication 3 days after discontinuation	Slightly impaired	Slightly impaired
Rote memory	"	No change	No change
Psychomotor tests	"	Increased speed less accuracy	-
EEG	14 days on medication	Not consistent, tendency toward slowed alpha frequencies	
		Increased & decreased alpha percentages	Decreased alpha frequencies & occasional delta in 2 of 6
	5 days after discontinuance	Normal	Normal

Siler (189) in 1933 reported on the results of an experiment in which marihuana cigarettes were freely available to 34 subjects for an average of six days. The daily mean consumption was 5 cigarettes per day (range 1 to 20). No abstinence symptoms nor ill effects were noted.

In a recent preliminary study (199), oral marihuana extract was administered to eight terminal cancer patients (age range 20-78; mean 53.4 years) daily for from 4-13 (mean 8.5 days). Calculated daily doses of THC were progressively raised by the investigator from 7.5 mg to a maximum of 52.5 mg with a mean dose of 19.8 mg THC per daptient per day. Total THC dose per individual patient ranged from 75-210 mgs with a mean of 168 mg. All eight patients experienced euphoria, 1 of 8 had an episode of acute anxiety, 3 of 3 gave objective evidence of pain relief as measured by decreased opiate analgesic requirements, 5 of 8 reported improved appetite, 4 of 8 had mild hallucinations at the higher drug levels, and 5 of 6 demonstrated improvement in depression (Beck scale). No significant changes were found in physical condition, neurological status and a wide range of blood and urine laboratory findings were unchanged. Minimal ill effects were noted and potential therapeutic effects were demonstrated. Therapeutic effects found were decrease depression, increased appetite and analgesia. There was no evidence of physical dependence and no abstinence symptoms were reported after abrupt discontinuation of the drug. Although drowsiness was common, lethargy, lassitude and indifference were not noted.

Mirin (152) has studied a group of male heavy marihuana smokers who had used the drug for an average of 4.4 years about 20 to 30 times a month. For 3 of the 4.4 years (range ½-5 years), they had smoked virtually every day. Another group of casual marihuana smokers, comparable in age (25 years),

educational experience (1 year graduate level), racial distribution (predominantly white) and social class (parents of higher socio-economic backgrounds) used marihuana 1 to 4 times a month for less than 2 years. Heavy marihuana use appeared to be correlated with: psychological dependence, search for insight or meaningful experience, multiple-drug use, poor work adjustment, diminished goal directed activity and ability to master new problems, poor social adjustment and poor heterosexual relationships.

Meyer (144) has been able to compare the effect of smoked marihuana on these two groups in the laboratory. In preliminary experiments, subtle differences are observed which may indicate the presence of tolerance to some of the effects of smoked marihuana in heavy (daily) users. The total quantity of marihuana consumed to obtain a "very high" state judged subjectively was slightly less for the heavy user group (3.1 mg THC for heavy vs. 37.8 mg THC for casual group)-not a statistically significant difference. The heavy users showed smaller pulse rate increases and less subjective and mood effects. Minimal to no impairment was seen in the heavy user group on perceptual and psychomotor performance tasks while the casual users showed decrements in these functions. The findings are generally consistent with the differences in performance noted in naive and chronic marihuana users by other investigations (39, 40, 108, 134, 218).

Health Consequences for the Individual of Marihuana Use

In this section, health consequences will imply any toxicity which is directly related to consumption of the drug, marihuana or to related substances. Toxic reactions are defined as any effects that result in physical or psychological damage, that the user subjectively experiences as unpleasant or that produce significant interference with adequate social functioning. Thus, the relaxed feeling of well-being or "high" is not considered toxic. Three factors are relevant to toxicity: the drug itself, including dose, frequency and duration of use; the personality, mental state and mood and expectations of the individual; and the setting or environment of drug use (193).

Short-Term Effects

The acute physical effects of marihuana intoxication including bloodshot eyes, burning or itchy eyes, dry mouth, excessive hunger, lethargy, rapid pulse have been discussed in previous sections and will not be repeated. These are minor effects of the drug and should not be considered major toxic reactions. The acute mental effects of the intoxication, including a variety of perceptual alterations, short-term memory loss, temporal disorientation, and depersonalization considered toxic reactions by many are frequently desired by the user. Such subjective reactions may sometimes progress to acute anxiety attacks and even acute psychoses in some cases. It is noteworthy that these acute physical and mental effects consistently appeared in the scientific literature of the late 19th century

as a "toxic manifestation" of medical use of cannabis preparations. (127)

Ungerleider, et al. (208) in 1968 reported a survey of 2700 psychiatrists, psychologists, internists and general practitioners in Los Angeles for adverse reactions to hallucinogenic drugs. "Adverse reactions" ranged from mildly unpleasant parental objections to severe anxiety or acute psychosis. Although 1887 "adverse reactions" were reported among these patients, the actual role of hallucinogenic drugs in causing the symptoms is not clear. The major implication of the study is that, among persons who are receiving professional help for personal problems, drug use mixed with personality dysfunction is frequently found.

The Haight-Ashbury Free Community Medical Clinic over a two year period from its opening in the summer of 1967, has treated over 40,000 young people for medical and psychiatric problems (193). These people include college students, professionals, working class people, as well as members of the Haight-Ashbury Free Community. 90 to 95% of its clients have had experience with marihuana (192). Smith (192, 193) has reported on the acute and chronic toxicity of marihuana in this population. Smith states that the role of the drug itself is overemphasized as a factor in toxicity.

Physical damage directly resulting from marihuana use alone is unproven at present (192). Although a few scattered reports of deaths associated with cannabis use are to be found in the literature, (17, 49, 62, 90, 101)

there have not been any reliable reports of human fatalities attributable purely to marihuana (193). Huge doses have been given without causing death and the median lethal dose has not been established in man. (19) Most of the fatalities are reports from Indian experience in the 19th century with large oral doses of charas (hashish).

A recent case report (100) presented the association of eating large amounts of marihuana over a 3 day period with the occurrence of severe diabetic coma and ketoacidosis in a young male without a family history of adult onset diabetes. The patient had not previously exhibited any symptoms of diabetes. No other precipitating factors were evident. The author speculates that the stress of marihuana ingestion may have been greater than the adaptive capacity of a marginal glucose regulating system. It is difficult to interpret the significance of such isolated case reports.

Other reported cases (78, 87, 116) relate severe physiological disturbances following intravenous injection of boiled suspensions of cannabis in multiple drug users. Chills, muscle aches, weakness, abdominal cramps, slowed respiratory rate and low blood pressure were uniformly observed. Other patients experienced diarrhea, vomiting, very rapid pulse, elevated body temperature, enlarged spleen and liver, pulmonary congestion and abnormal kidney function. These symptoms are believed to be primarily due to the reaction to intravenous injection of a foreign material.

Some of the most common toxic reactions which have been encountered at the Haight-Ashbury Medical Clinic are nausea, dizziness, and a heavy,

drugged feeling where every movement required extreme effort (193). These reactions represent getting "too stoned." Most frequently, they occur with oral consumption or in inexperienced marihuana smokers. Due to the rapid onset of psychoactive effect, smoking usually allows the experienced individual to control or "self-titrate" his dose to achieve a desired "high." Thus, he is able to stop smoking at the first sign of subjectively defined unpleasant effects. This ability to control dose and effect is not available to the inexperienced smoker or when the drug is consumed orally.

Another factor may explain the clinical observation that heavy chronic users of marihuana can tolerate higher doses without encountering acute (physical and mental)toxicity. This factor is tolerance. Smith (193) suggests a "J" shaped time curve of tolerance to marihuana. A novice exhibits a moderate degree of tolerance. With increasing experience with the drug, he "learns to get high" causing a reverse in tolerance. That is, he requires less drug to reach his desired high. With chronic heavy use, tolerance increases again.

Some (119, 138) have suggested that a biochemical phenomenon accounts for tolerance and reverse tolerance. Possibly the enzyme necessary to metabolize Delta-9-THC to an active agent requires some prior marihuana use to develop sufficiently. The maximum attainable quantity of this enzyme may be the factor that controls the development of tolerance with chronic use.

Whatever the cause, the evidence suggests that mild tolerance to cannabis develops with chronic use of large doses (35, 51, 62). However, more moderate use for many years may not necessitate increasing doses (188). It is doubtful that Indian ganja and charas smokers could consume an estimated 720 mg THC average daily dose without having developed some degree of tolerance (35). Other investigations have found that smoked doses of 20 mg THC and 70 mg Delta-9-THC orally often produce dysphoric reactions in experienced but non-heavily using marihuana smokers. (105, 134)

Both Weil (216) and Smith (192) believe that non-drug factors play the most important role in the occurrence of acute toxic reactions. That is, the effect of marihuana on the individual depends to a large extent on the interaction of drug effect with the individual's psychological make-up, expectations, attitudes, mood and the physical and emotional circumstances surrounding drug use. The great variability in these factors makes the effect of marihuana rather unpredictable in many circumstances.

50% of the acute toxic cases in the Haight-Ashbury Medical Clinic (193) and 75% of those seen in hospital practice by Weil in Boston and San Francisco represent "novice anxiety reactions" or panic reactions (216). In these cases, the individual interprets the physical and mental effects of the drug to indicate he is dying or "losing his mind." The large majority of these occur in novices who often have strong underlying anxiety surrounding marihuana use such as fears of arrest, of disruption of family and occupation relations, and/or of possible physical and mental dangers.

The majority of these reactions appear to occur in people with relatively rigid personality structures (193). In the presence of psychological stress, simple transient neurotic depressive reaction may occur in these same types of individuals. According to experienced clinicians, both these types of reactions are transient and require simple, gently but authoritative reassurance that nothing is seriously wrong with the user and that the drug effects will wear off in several hours (193, 216). Several other investigators reported a number of cases of this type (8, 9, 79, 82, 165, 188).

Numerous reports of cases of acute psychosis precipitated by cannabis use usually associated with existing stress have recently been reported in the literature (5, 20, 21, 86, 100, 105, 110, 134). However, these appear to be relatively infrequent under most conditions of casual use (113, 193, 216). These psychotic episodes may occur in persons with a history of mental disorder, in individuals who are marginally adjusted or in those who have poorly developed personality structures (192). The marihuana intoxication may hinder the ability of the individual to maintain structural defenses to existing stresses or else produce a keener awareness of personality problems or existing stresses in the individual. Psychotherapy and antipsychotic medication are useful in the control and prevention of these reactions (216).

Weil (218) reports an exceptionally rare occurrence of nonspecific toxic psychosis or acute brain syndrome occurring after an oral overdose

of marihuana. He believes that certain toxic constituents of cannabis may get into the body when the substance is eaten but which are destroyed or non-volatilized in the smoking process. This type of reaction has, however, also been reported in the eastern experience to accompany increased amounts of smoked cannabis over a short period of time (11). These toxic psychoses appear to be self-limited. Similar reports of brief, self-limited psychosis have been observed during experimental administration of high doses or oral marihuana or THC. (6, 106, 134, 223)

Weil (218) also reports marihuana intoxication may trigger a delayed psychotic reaction in a small percentage of persons who have previously taken other hallucinogenic drugs. Since such reactions may occur without subsequent marihuana use, the exact role of marihuana in precipitating them is uncertain.

Dependence and Withdrawal

Sedation and sleep are the immediate after effects of acute intoxication, especially when used in the evening. Williams (223) reported increased amount of time spent sleeping during chronic use. Pivik, et al (167) have reported that oral administration of 20 mg Delta-9-THC or marihuana extract slightly decreased total Rapid Eye Movement (REM) time in two sleeping subjects. However, Rickles, et al (177) have presented preliminary data suggesting a subtle effect on sleep time. He found that four marihuana smokers who used one or two cigarettes per day for at least one year often in the evening, demonstrated a slight increase in total REM sleep time.

This total increase was primarily due to a moderate increment in REM time during the last one-third of the night.

Most accounts of non-medical use report minimal hangover effects (134, 137, 223). After heavy use, some have reported feelings of lassitude and heaviness of the head. Lethargy, irritability, headaches and loss of concentration have also been reported, usually associated with large doses and lack of sleep. (35, 101)

Reports based on Indian experience suggest neither severe physical or psychic dependence, nor severe withdrawal symptoms even after abrupt termination of very heavy usage (29, 74, 124, 130, 189, 211). Evidence of possible physical dependence with physical withdrawal symptoms following discontinuation of heavy use and of appreciable psychic dependence is suggested by the Studies of the Indian Hemp Commission (101), Chopra (32) and Bonquet (18). Abstinence symptoms most reported were physical prostration, intellectual apathy (18), loss of appetite, flatulence, constipation, insomnia, fatigue, abdominal pain and uneasiness (117). Psychic dependence may, however, be an important obstacle to discontinuing cannabis use. For example, 65-70% of Soueif's (195) hashish users were reportedly unable to stop their habitual cannabis use although the average frequency was only 8-12 times per month. Studies in the U.S. using much lower doses for shorter time periods than Eastern studies have thus far found no evidence of psychic or physical dependence (21, 134, 223).

Chronic Physical Effects:

The only physical effect firmly linked to long-term cannabis use at present is permanent congestion of the transverse ciliary vessels of the eye and an accompanying yellow discoloration (6, 32, 52, 62). No other chronic physical damage has been satisfactorily demonstrated although there are other suspected or reported effects. It is noteworthy that many of the experimental studies of acute and chronic drug effects discussed earlier used as subjects individuals with at least one year and often longer histories of moderate to heavy marihuana usage. However, none were able to differentiate between these subjects and naive subjects with respect to physical or laboratory findings.

The LaGuardia report (134) of 1944 indicates no evidence of organic damage to the cardiovascular, digestive, respiratory and central nervous system or to the liver, kidney and blood in individuals who had used from 2-18 marihuana cigarettes (an average of 7) daily for a period of from 2½ to 16 years (an average of 8 years). Another less comprehensive examination of 310 persons with an average usage of marihuana of seven years duration concluded the subjects suffered no mental or physical deterioration (75). The Indian Hemp Drugs Commission (101) of 1894 reached the following conclusion: generally the moderate use of (cannabis) appears to cause no appreciable physical injury of any kind. Excessive use does cause injury. The report on cannabis in 1968 of the Advisory Committee on Drug Dependence of the United Kingdom (The Wootton Report) concluded after an extensive review "that the long-term consumption of cannabis in moderate

doses has no harmful effects." However, the Interim Report of the Commission of Inquiry into the non-medical use of drugs (102) concluded "there is hardly any reliable information applicable to North American conditions concerning the long term effects of cannabis." The results of studies in Eastern countries are of questionable applicability to North American conditions because of the significant differences in many of the variables determining drug effect. These differences include physiological and psychological condition of the people; conditions of nutrition, sanitation and climate; potency, drug dose level and frequency of use; and other drug use. The Canadian Commission stated there was no way of drawing comparisons with the Eastern levels of "moderate use" referred to by the Indian Hemp Commission and Wootton Reports and the levels of use that might occur in North America if the substance were freely available and socially accepted. The Canadian Commission also believed that the experimental design of the LaGuardia study was not up to modern standards so that its conclusions raised serious reservations. It lacked double-blind and placebo controls and adequate statistical analysis of data. The reporting of results was not entirely unbiased. Small numbers of subjects were used and the relevance of a prisoner sample to a more normal population has been questioned.

Bronchitis, asthma and a high incidence of respiratory problems are a frequently claimed effect of chronic use (35). The Indian Hemp Commission concluded that chronic and excessive smoking of ganja and charas could produce these conditions. It is noteworthy that Eastern smoking mixtures frequently contain both cannabis resin and tobacco. Mann (126) et al,

reported that modern electron microscopic methods able to discriminate pulmonary tree lining cells of non-smokers from tobacco smokers, detected no difference between non-smokers and long-term marihuana only smokers.

Indian users have been reported to exhibit a high incidence of digestive difficulties, diarrhea, constipation, weight loss and sleep disturbance (35, 195). However, the effects of poor living conditions and the prevalence of communicable disease may have been contributing factors to these symptoms in that culture.

Arteritis was found in a high percentage of heavy Morrocan Kif users (197). This may be related to the finding of tropic foot ulcers in chronic users (153). The significance, if any, of these scattered findings is at this time not clear.

Kew (116) has suggested a possible role or cannabis in mild liver dysfunction in eight persons who smoked marihuana for 2-8 years at least six times a week. Several of these patients also admitted to use of alcohol and oral amphetamines but denied that they used opiates or amphetamines intravenously. Liver function tests disclosed some evidence of mild liver dysfunction which was confirmed by minimal changes in liver biopsy on three of the subjects.

Mental Deterioration and Psychosis

The term mental deterioration covers many aspects of disturbed mental functioning, but for the most part studies fall into three major categories;

mental illness, brain damage, and the so-called amotivational syndrome.

For the most part, a connection between marihuana and mental illness, like those of a connection between marihuana and violence, is based on studies done in countries which are underdeveloped scientifically as well as economically. Most of these studies suffer from biased sampling, poor data collection techniques, and a failure to control for such important variables as level of nutrition, socio-economic status, overall standard of living, as well as cultural determinants. Many of these cultures do not sanction the use of alcohol. As a result the potentially drug dependent may turn to more easily available and less expensive cannabis preparations.

In evaluating the significance of overseas studies of the relationship of cannabis use to mental deterioration it is important to recognize the comparatively low level of attention that can be paid to psychiatric illnesses and to the fate of the mentally ill in countries where life for the bulk of the population is one of marginal survival and there are more pressing public health problems. Here crippling chronic illnesses long since eliminated in the West are still endemic, and mental hospitals and trained psychiatrists do not rank high on the list of national health priorities. Yet some of the most widely quoted studies in the literature on marihuana and psychosis have originated from poorly staffed and maintained psychiatric hospitals, operating with a minimum of professionally trained psychiatrists.

The Indian Hemp Drugs Commission paid particular attention to the question of possible mental deterioration connected with cannabis use,

since at the time it was formed the common impression was that consumption of hempdrugs (particularly to excess) produced insanity. In addition, statistics from Indian mental institutions were widely quoted to support the connection between cannabis and mental illness.

From the standpoint of modern scientific methodology, the Indian Hemp Commission report can be faulted in a number of ways, but in its examination of the relationship of cannabis to psychoses, this work is still impressive for its thoroughness and objectivity.

The Commissioners questioned the popular impression that marihuana use leads to insanity because "the unscientific popular mind rushes to conclusions and naturally seizes on that fact of the case that lies most on the surface." They noted that in England itself there were wide variations between hospitals in the frequencies of the various types of mental diagnosis. In India, a good part of this variation was found to arise from the fact that diagnoses were made on the basis of a "descriptive role" that was sent to the hospital at the time the patient was admitted. This "descriptive role" was typically filled out not by a psychiatrist, or even a physician, but by a magistrate or a policeman. Since neither the magistrate nor the policeman had the capacity to make an accurate diagnosis, they frequently used the diagnostic category of insanity due to excessive consumption of hemp, for lack of any more obvious cause.

The Commission, convinced of the unreliability of the existing hospital statistics, examined all admissions to Indian mental hospitals in

one year, 1892, in order to make its own diagnosis. Of 1344 admissions, the commission found that cannabis consumption could be considered to be a factor in no more than 7-15% of the cases. (101)

A second major study done in India by the Chopras examined mental hospital admissions in India from 1928 through 1939, and found only 600 cases which could be traced solely and unambiguously to the use of cannabis. At the time this study was done, the number of users of cannabis of all types was extremely high in India. (36)

South African mental hospitals have reported about 2 to 3% of their admissions due to dagga smoking, and in Nigeria 14% of psychiatric admissions were users and one half of these were cannabis related.

Studies based on several hundreds of cases indicate that the large majority can be classified as acute psychoses, and are associated with a "sharp toxic overdose" or with "massive excesses" among habitual users. The clinical picture is that of a severe exogenous psychosis - delirium with confusion, disorientation, terror or anger, and subsequent amnesia about what happened during the period of intoxication. (36)

Eastern authors uniformly report fairly short recovery times ranging from a few days to six weeks. This is in sharp contrast to the lengthy recovery period typical of the functional psychoses.

The symptomatology of the acute psychosis is highly varied and often similar to schizophrenia at the outset. Several studies have called attention to the confused, manic aspects which frequently characterize the state and sometimes lead to impulsive acts of violence. These clinical manifestations are particularly important in any attempt to assess the overall prevalence of psychoses among cannabis smokers through examination of mental hospital records. Socially disruptive behavior in both Eastern and Western countries is still a prime predictor of possible hospitalization for mental illness. Although the symptomatology of the acute psychosis is highly varied and often similar to schizophrenia at its onset, the acute cannabis psychosis does not typically involve the type of thought disorders characteristic of schizophrenia. Thus, it appears that this acute cannabis psychosis described in the Eastern literature is similar to the acute toxic psychosis currently being reported at lower doses in less chronic marihuana users in the Western World.

The existence of a more long lasting cannabis-related psychosis is less well defined. There appears to be some evidence to support the existence of a slow-recovery, residual (2-6 months) cannabis psychosis following heavy chronic use. The symptoms developed gradually tend to subside rather than developing into full-blown psychotic systems. Long-term patterns of acute and subacute psychotic episodes accompanying continued heavy use have also been described. These may produce gradual psychic deterioration in habitual excessive users after prolonged periods of time. Western experience has involved a level of cannabis usage substantially below that of these Eastern studies and the associated psychic disturbances are not generally comparable.

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Other Mental Effects

Another group of symptoms that have been described on a worldwide basis as associated with heavy chronic cannabis use is called the amotivational syndrome. (32, 36, 38, 101, 182, 212) In its extreme form it represents a loss of interest in virtually all other activities other than drug use - lethargy, social deterioration and drug preoccupation that might be compared to that of the skid row alcoholic's preoccupation with drinking in the Western world. The meaning of the term is however somewhat unclear. Some have used it as a kind of blanket description to encompass a range of passivity as well as to include the behavior of numbers of young Americans who are for various reasons dropping out of school and refusing to prepare themeselves for more traditional adult roles. Recently chronic American use has been associated with a type of social maladjustment resembling that reported in the foreign literature. (152) Smith describes such a syndrome as "a loss of desire to work, to compete, to face challenges. Interests and major concerns of the indivdual become centered around marihuana and drug use becomes compulsive. The individual may drop out of school, leave work, ignore personal hygiene, experience loss of sex drive and avoid social interaction." (192)

A possible milder variation of this syndrome has recently been described by Scher in normally functioning members of the society who used marihuana for at least five years continuously throughout the day. These individuals begin to experience a vague sense that something is wrong and that they are functioning at a reduced level of efficiency. (186)

The question of whether there exists a significant casual relationship between cannabis and amotivational syndrome or only an associative or correlational relationship of a person possessing these traits and cannabis use, remains to be answered.

West has described a clinical syndrome as a result of observations of regular marihuana users for 3-4 years. It is his clinical impression that many of these individuals show subtle change of personality over time, Noted are: "diminished drive, lessened ambition, decreased motivation, apathy, shortened attention span, loss of effectiveness, introversion magical thinking, derealization and depersonalization, diminished capacity to carry out complex plans or prepare realistically for the future, a peculiar fragmentation in flow of thought, habit deterioration, and a progressive loss of insight." West feels that in this configuration of symptoms a possible organic syndrome is involved. (19, 219)

Recently another group of investigators (71, 221) has reported tentative and preliminary data on a group of nineteen hospitalized young (14-20) patients suffering from behavior disorders. Eight of these had used only marihuana rather heavily, the other eleven marihuana in addition to other drugs such as LSD and amphetamines. Characteristically these patients showed a loss of movivation to pursue school work and other constructive activities. Other symptoms included regression to " primitive and magical modes of thought" and a low frustration tolerance. Sixteen of the group showed subtle abnormal EEG patterns particularly related to the temporal lobes. These researchers

were struck by the similarity between these abnormal brain wave findings in a group of cats administered a marihuana extract intraperitoneally. The nature of the patient group, the uncertain drug histories and the heightened likelihood of abnormal EEG tracings on other grounds all lead these investigators to interpret their work with caution. They do, however point out that both their human and animal data tend to bear out, although not yet proven, their original clinical impression that heavy marihuana use may be an important factor in altering brain function and thus contributing to the abnormal behavior they observed. They and a number of other researchers are continuing to study the relationship of marihuana use to possible alterations in brain function.

Another possible psychological effect of marihuana is the spontaneous recurrence without ingesting the drug of effects like those experienced when intoxicated. Such recurrent effects commonly called flashbacks have been widely reported for LSD. While such flashbacks with marihuana have been reported (110), truly vivid experiences that recapture most of the elements of the original experience are thought to be extremely rare at least in the type of chronically using marihuana population seen in the Haight-Ashbury Medical Clinic. (193) Such flashbacks may be most likely to recur following a particularly adverse drug reaction and may more closely resemble a recurrent anxiety state that the total original drug experience. Some disagreement on this point may well reflect differences of opinion as to how vivid and complete the recurrent experience must be to be termed a flashback. Many users, for example, report that new perceptual awarenesses which occurred while "high"

may persist following it. If one accepts any even mild recurrence of any aspect of the drug experience without again ingesting the drug as a flash-back phenomenon, that such experiences may be relatively common.

Weil (216) reports the recurrence of hallucinogenic experiences during marihuana intoxication in several individuals after occasional use of LSD or mescaline. These people found that their marihuana highs changed after their hallucinogenic experience, becoming benign and pleasant in some instances but disturbing in others. Ungerleider (209) reported marihuana use recreating the LSD experience months after the LSD experience. Favazza (64) reported another case of marihuana triggering the recurrence of a frightening LSD episode. There is no way of knowing whether these LSD flashbacks would have occurred without marihuana.

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SOCIAL AND CULTURAL CONCOMITANTS OF MARIHUANA USE

The Progression Hypothesis

The Substitution Hypothesis

Cannabis and Crime

SOCIAL AND CULTURAL CONCOMITANTS OF MARIHUANA USE

Although data concerning the social and cultural concomitants of cannabis use is inadequate in many respects, there are certain social constants concerning the moderate smoker which seem to hold true across a variety of studies conducted in many countries. The marihuana smoker tends to be young, male, and up until the present time, was predominantly drawn from members of lower socio-economic groups. There are no adequate figures available as to how long the moderate marihuana usuage pattern persists, or as to how many of the moderate users progress to heavier use of cannabis, even apart from their possible progression to stronger drugs.

In the United States, marihuana smoking tends to be a group activity, and group members are persons who have more than a casual aquaintance with one another - in sociological terms, the group is composed of significant others.

Induction of a neophyte into the use of the drug is ordinarily the province of a close peer, who socializes him into expectation of a pleasurable experience, and allays his dismay (if the initial experimentation turns out to be frightening or disagreeable) or continues to feed his hopes (if it does not prove to be as pleasurable as expected) by assuring him that it is all part of a learning experience. Females are quite frequently introduced to marihuana smoking by male companions.

Cannabis smoking itself has significant social elements of sharing, with ritual overtones. Even the fact that individuals seem to be oblivious of one another once the desired degree of high has been achieved, should

be considered in the context of the comfortable silences possible only among close friends.

Although the number and types of marihuana smokers in the United States are too diverse to be called a true subculture, it is a fact that within each of the diverse groups who use the drug, there is a shared value system, of which cannabis use is only one part. Groups with very diverse value systems, for example motorcycle gangs like Hell's Angels and hippie residents of the early Haight-Ashbury, would both use cannabis, but obviously in the context of very different life styles.

But whatever the diverse value systems of the different groups of cannabis users the major presenting social fact to those charged with the protection of the nation's health, is that cannabis use tends to be an activity of the young, drawn from all social classes. It is comparatively easy to identify the population most at risk, but there is, at present, no completely clear definition of the most relevant parameters of risk, both for the individual and for society.

In the case of a society, it is possible, on the basis of even so gross a measure as the volume of research published in certain particular areas, to sketch out at least a preliminary outline of a risk hierarchy concerned with moderate cannabis use, and another such hierarchy concerned with excessive and/or chronic use.

So far as a community, or a society is concerned, three of the major areas of interest for moderate cannabis use have been these:

1. The possiblility of progression to the use of either more or stronger marihuana, or to other stronger drugs (whether they be hallucinogens or narcotics);

2. The possibility of the development of psychic dependence and/or psychotic reactions:

3. The possibility of the commission of crimes while under the influence of cannabis.

Among the reputed effects of marihuana mentioned in many discussions in past years is that of progression to stronger drugs, especially the opiates. The usual explanation has been that marihuana use develops a "taste for drug intoxication" which leads to trying stronger drugs. There have been numerous debates on the subject. Now it is generally agreed that whatever association exists between use of marihuana and other drugs for a particular group must be examined for contingent or qualifying conditions.

More recently, it has been argued that marihuana use can substitute for use of alcohol. The explanation has been that marihuana provides relaxation and euphoria, as alcohol does, but in having less unpleasant side effects, will be seen as more desirable.

The first of these assertions (the progression hypothesis) has been detailed with evidence from several kinds of studies: compilation of hospital and prison records, sample surveys, and interview studies of selected populations. None, however, has been a prospective or longitudinal study designed specifically for the purpose of testing the progression hypothesis or, for that matter, the substitution hypothesis. Thus, conclusions about the relationship are based on evidence that is far from ideal for the purpose.

Recent observations that heavy involvement with drugs usually involves simultaneous use of two or more drugs in more or less planned patterns, should lead to a change in the question itself. That is, it should no longer be assumed that drug use always develops seriatim, the user being on one drug until he turns to another. The research question perhaps should be: Under what social, or psychological conditions do persons use drugs of different kinds in various combinations and patterns?

1. The progression hypothesis

Long before the recent debate over this effect, the Indian Hemp Commission of 1893-94 found no evidence in the Indian population that marihuana use was a stepping stone to the use of opiates in any substantial number of people. It has been observed and reported innumerable times that American narcotic addicts in most cases have used marihuana before becoming addicted to the stronger drugs. This fact, by itself, has been convincing to many. Among the heroin users studied by Chein, for example, 83 of a total of 96 had used marihuana previously. (9) In a study by Chapple, it was concluded that the connection between marihuana use and heroin addiction could not be accounted for simply on the basis that both drugs were available from the same illicit source. (7) Although the authors' conclusions did not actually favor the progression hypothesis, a study by Ball, Chambers and Ball was cited frequently to show that over 70% of the addicts in the study had used marihuana prior to their use of heroin. (1)

Gradually recognition has come that the answer to the question lay in more clear formulation of the problem. Richard Blum stated in the Task Force Report of 1967:

With reference to the belief that marihuana causes heroin use in the sense that it predestines its user to go on to bigger things, there are two critical tests: one asks what proportion of marihuana users do not go on to heroin; the other test asks if marihuana use is an inevitable and necessary precondition of heroin use, that is, can it be shown (a) that all heroin users first took marihuana, (b) that such marihuana use is the only factor common to heroin users, and (c) that the presence of this common factor can be shown experimentally to be a determinant of heroin use. The results of such tests are, of course, negative. Most persons who experimented with marihuana do not try heroin, some heroin users even in slum cultures... have not first tried marihuana, and among heroin users first trying marihuana a number of other common factors are also likely to be present. Among these may be experimentation with other illicit drugs reflecting a general pattern of drug interest and availability (3).

A test of the last of the above hypotheses was carried out by Robins et al. on retrospective data collected from Negro men in their early thirties. (18) Only a minority of marihuana users went on to try heroin; and drinking in turn usually preceded marihuana use. Marihuana use was associated with later alcoholism, however. The authors speculated that marihuana use may increase the risk of alcoholism, which itself appeared to account for some of the other adult troubles seen among those who also used marihuana.

The Ball, Chambers and Ball study should be summarized since it is so often cited and represents other studies in which opiate addicts are the initial group for investigation (1). These authors examined records and interviewed a portion of a sample of addicts admitted to Lexington and Fort Worth hospitals during 1965. They found not one but several patterns

of association between marihuana and opiate use. One was a positive association found in sixteen States with high addiction rates. This was seen among those individuals who were apt to be deviant on most variables - arrest record, early arrest, earlier onset of opiate use, intravenous administration of opiates, heroin use, and obtaining drugs from underworld sources. The other pattern was a lack of association between marihuana smoking and opiate use, found in twelve Southern States where also, opiates other than heroin were more typical. The authors concluded that the smoking of marihuana cigarettes does not necessarily lead to opiate addiction, but suggested that marihuana smoking had increased among opiate addicts in the U. S.

In one large student survey, evidence was clear that marihuana smoking was associated statistically with use of other drugs (4). More students had used it than any other illicit drug, though not more frequently than alcohol or tobacco. And more than any other illicit drug, it was correlated with other illicit drug use. Blum said in 1968, "Although there is still no evidence of any causal 'stair-step' effect such as that marihuana use leads to heroin, evidence does indicate ... that an initial interest in drugs, which is necessarily expressed in taking one of many possible illicit-exotic substances, can lead to expanding drug interests and commitment to a life style in which drugs play a predominant role."

The details of relationships between drugs are being spelled out in recent reports. Some show that heavy (frequent, regular) use of a given drug (such as marihuana) is much more likely to be associated with use of

other drugs than is light use or experimentation. In one study of college students, for example, the following percentages of users in each category of marihuana use had used other drugs: (10)

100% of daily marihuana users had used other drugs
84% of weekly marihuana users had used other drugs
22% of monthly marihuana users had used other drugs
20% of marihuana experimenters had used other drugs
0% of marihuana abstainers had used other drugs

Other drugs tried in order of frequency were: hallucinogens, "downers," "uppers," hashish, and hard drugs. Another study of nine campuses produced a similar finding: that the heavier the involvement with a given drug, the more likely it was that the student was involved in more than one drug (16).

These studies seem to point toward a "drug proneness" factor. In fact, Blum's factor analysis of students' use of all drugs measured on five campuses indicates just that: "a general disposition toward psychoactive drug use . . . (that) . . . reflects the widespread willingness to use a variety of drugs as tools to alter states of consciousness, biological cycles, and social relations " (4). Blum also found two subsets of dispositions linking particular drugs. One factor was identified as style of drug use by source; the separate components were 1) conventional social-drug use, such as alcohol and tobacco and 2) the employment of illicit-exotic substances, expecially marihuana and the hallucinogens. Less clearcut was a style of reliance on prescription drugs. The place of opiates in this analysis was also unclear, but the proportion of the student body using opiates on any campus was miniscule— 1-2%.

Findings from a recent study of marihuana smokers, mainly white middle-class, are consistent with a developing theory of multiple drug use.(11) The most potent variable in determining use of drugs other than marihuana is how much the person smokes marihuana. At that point, heavy marihuana use, according to the author, tends to "implicate the individual in intense and extensive social interaction with other marihuana users," involves him with numerous marihuana users and in numerous marihuana-related activities, alters the role of marihuana as a relevant criterion in his conceptions of others, and changes his conception of himself as a drug user. Moreover, it increases the likelihood of his taking drugs, in addition to marihuana, of which the subculture approves. In middle class groups, the approved drug would most likely be LSD; in ghetto groups, heroin.

The above hypothesis was confirmed in another recent study that by chance had a preponderance of black over white respondents (12). In a group of marihuana users who had not used heroin at the time of the study, those who had had an opportunity to try heroin tended more often to be black, to have tried other drugs, to know heroin users, and be intensive users of other drugs.

In the next few years, more will be known about the chronological sequence of multiple drug use and some of the factors associated with changing use patterns. One study to begin in 1971 will be a longitudinal study of junior and senior high school students over a period of years, in which a determination will be made of sequence and duration of use of both illicit and legal drugs (20).

2. The Substitution Hypothesis

The possibility that marihuana might serve as a substitute for alcohol has been suggested most often by drug "advocates." The common argument about the relative harmlessness of marihuana and alcohol implies in part that the former would be preferred and chosen instead of the latter. Almost all surveys where measures of use of both drugs have been cross-tablulated have shown, however, that there is clearly an association between drinking and using marihuana./ (2,4) (Usually use of tobacco is also associated.) The association is statistical, not causal, and questioning has not been designed to show whether drinking preceded, accompanied, or followed the use of marihuana. Indeed, it may simply reflect the fact that marihuana users, based on education and family background, are less traditional or conservative in several respects. It is known though that for almost all adolescents, the first psychoactive drug was alcohol or tobacco.

Findings on the use of the two drugs in a follow up study in San Francisco has been reported as a reversal of the marihuana-alcohol relationship, however. There, marihuana users report less use of alcohol (15).

More extensive analysis of existing data and inclusion of these variables in future studies will illuminate these relationships.

3. Cannabis and Crime

The arguments relating cannabis to crime generally fall into three major categories: 1. Loss of control during intoxication and indulgence

in impulsive and irrational acts of violence, particularly in the case of a psychotic reaction; 2. Loss of a sense of moral discipline and inhibition, an increasing number of associates drawn from criminal ranks; 3. Direct contribution to crime by fortifying the criminally inclined to commit anti-social acts.

It is of interest to note that the Indian Hemp Commission, as far back as 1893, devoted itself to a consideration of all of the issues mentioned above, under the terms of its mandate which had to do with the effects of the consumption of hemp drugs on the "social and moral" conditions of the people.

In attempting to reach conclusions about the involvement of marihuana users in violent crime, the Commission first distinguished between the moderate and the "excessive" user. Even in India at the time of the report, when there was a greater overall number of users, when the cannabis preparations in use were apt to be much stronger than the type used in the United States today, the greatest proportion of users tended to be moderate users.

The Commission began by asking approximately 1400 witnessess, drawn from diverse regions of India, this question: "Are consumers of cannabis offensive to their neighbors?" The theory behind the use of this question was of course, the idea that this kind of a query would serve to elicit any mention of aggressive or violent behavior, since these behaviors would be offensive to their neighbors. Only about 700 of the witnesses stated

that they knew anything at all about the issue; which would lead one to conclude that they had not had any experience with offensive behavior on the part of their neighbors. Of the seven hundred witnesses who said that they did have some knowledge of the issue presented, six hundred stated that moderate consumers were not offensive to their neighbors and could not be distinguished from total abstainers. Of the one hundred witnesses who did find cannabis users offensive, most were referring to heavy users, and even so they were not speaking of aggressive behavior,, but of behavior such as "excessive coughing or expectoration," or the bad examples set to neighboring children.

When the issue was put even more precisely, and the Commission asked the witnesses direct questions about crime, a majority of the witnesses (8 to 1) held that moderate consumption of these drugs had no connection with crime in general, or with crime of any particular character. This is not to deny that some users of cannabis did commit crimes, but it should be borne in mind that the majority of cannabis users in India were drawn from the lower classes and the crime rate in this group (particularly the rate for violent crimes) then, as now, was higher than it was among the middle and upper classes.

In any event, the social threat of cannabis-induced violence rests not so much on the demonstration of the existence of a relationship, but on the prevalence of such violent incidents. The Indian Hemp Commission concluded that the overall incidence of cannabis-induced violence was negligible.

A good deal of the material on cannabis use in present day India relies on the research work of the Chopras, three physicians who have been writing about various aspects of cannabis consumption in their native country for the past thirty years. The Chopras' most recent statement, largely a summary of their previous work, (8) asserts, "With regard to premeditated crime, in some cases the drugs (bhang, ganja and charas) not only do not lead to it, but actually act as deterrents. One of the most important actions of cannabis is to quiet and stupefy the individual so that there is no tendency to violence."

Literature from Eastern countries, unlike that emanating from the West, provides some evidence that cannabis connected and/or supposedly cannabis-induced psychotic reactions are often accompanied by "excitation and impulsivity liable to produce serous anti-social reactions. (19) It is likely that disruptive behavior plays a significant role in determining whether or not an individual with an acute cannabis psychosis is hospitalized. This behavior is most likely to be perceived and dealt summarily, if the individual exhibiting it is a member of a lower socio-economic group.

One comparatively early study (1938), (17) is of particular interest in regard to cannabis and certain types of violent reactions. Investigators in South Africa administered dagga to hospitalized psychiatric patients and found that 35% of them exhibited marked motor excitement and were extremely irritable and assaultive. This is in marked contrast to the typical cannabis reaction of quiet euphoria and lassitude, and suggests the possibility that hyper-excitability and impulsive behavior may not be an

uncommon reaction in severely disturbed individuals.

In the United Kingdom, theWootton Commission stated (1968), (6), "The taking of cannabis has not so far been regarded, even by the severest critics, as a direct cause of serious crime." The LeDain Commission, in Canada, came to similar conclusions.

There have been few statistical studies which have addressed themselves to the overall incidence of detected crimes among cannabis users, but on balance they tend to show an associational basis between cannabis use and minor asocial or anti-social behavior, not between cannabis and major crime. Those studies which begin with a sample of persons arrested for cannabis offenses generally show a much higher positive correlation with other delinquent behavior than do studies which begin with a more representative sampling of cannabis users. One study of the latter type is the one conducted by Richard Blum on five college campuses in the late sixties. Blum found, among his college respondents, that of the 19% who said they had used marihuana, only 1% reported getting into fights while under the influence of the drug. This was in marked contrast to the statements about alcohol. About 94% of the total sample had tried alcohol, and 8% of these reported fights after drinking.

In the United States, we have had far fewer studies devoted to cannabis use among members of lower socio-economic groups and members of minorities than studies of marihuana usage on college campuses. One of these studies, however, The World of Youthful Drug Use, by Professor Herbert Blumer and his associates of the University of California, is a very comprehensive examination of the relationship between drug use and life style in general of members of deprived groups. This study indicates that although examples

of violent crime, delinquency and arrests are far more common among deprived Mexican-Americans and Negroes than among college students, marihuana is no more likely to be associated with aggressive acts in this population than it is in the college population.

The Blumer study found that for the most part the population studied could be divided into two major culture groups - the "rowdy" and the "cool." The member of the rowdy group may be characterized as "aggressive, boisterous, wild and undisciplined. He is disposed toward fighting, seizes on any drug, but prefers alcohol, and is ready to engage in the more serious and violent forms of delinquent behavior." The rowdies use marihuana, as do most other youths in the ghetto, but their use seems to be considerably less than average in this population. It would seem that the so-called calming effects of marihuana do not fit in with their personalities or their preferred life styles and they turn to other drugs.

The "cool" culture, according to Blumer, means "being unruffled in critical situations, keeping one's head, acting wisely, showing calm courage, controlling one's voice and behavior, being smart and not provoking trouble, but being able to handle oneself calmly in troublesome situations." A considerable number of youngsters make their way from the rowdy group to the ranks of the cools, and Blumer reports that "the passage from the rowdy type to a cool and mellow youngster, as it relates to the use of drugs, involved chiefly a shift to the smoking of marihuana." The young informants themselves believed that marihuana both produces and symbolizes a mellow mode of conduct that is opposed to that associated with rowdy behavior.

One of the most meaningful, if not the most meaningful ways of assessing the contribution of cannabis to aggressive behavior, and to crime and violence, is through a comparison with alcohol. The latter provides an established baseline through reliable statistics, as well as through everyday experience. Authors throughout the world when comparing the properties of alcohol and cannabis almost invariably conclude that the former is much more likely to be associated with violence.

In summary, and on balance, it would seem that cannabis use is a relatively minor contributor to major crimes and violence in any country in the world in which it is used.

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RESEARCH NEEDS AND FUTURE DIRECTIONS

RESEARCH NEEDS AND FUTURE DIRECTIONS

This section is intended to give some indication of future research needs and of the Department's program to provide the data needed to adequately explore the health implications of marihuana use. It should be emphasized that the issue of marihuana use in our society is complex and also involves moral, philosophical and legal questions which are unlikely to be resolved by scientific research. Whatever the ultimate resolution of these issues of values, it is essential that there be adequate understanding of the health implications of millions of Americans using marihuana in order that the individual and the society may more rationally approach the issue.

In retrospect, much has already been accomplished in expanding our understanding of marihuana since the Department, through its National Institute of Mental Health,embarked on a high priority marihuana research program. An adequate supply of well standardized natural and synthetic materials has been developed and a comprehensive program of research is currently being supported. The results of some of this ongoing research are summarized in this report. As time passes, additional information will become available so as to provide a more complete picture of the implications of marihuana use at various dosage levels and in differing use patterns.

While much has already been learned about the chemistry and the acute physiological effects of cannabis and related synthetics, much remains to be learned. More careful study is needed of the known psychoactive compounds, how they are metabolized and the role of their metabolic

products in producing a range of acute and chronic effects. It is also important to understand the possible influence of other constituents of cannabis which may not in themselves be psychoactive but may nevertheless influence the action of those constituents which are.

The question"what is the active component of marihuana" has been partially resolved. Delta-9-THC, probably acting through a metabolite (11-hydroxy-THC) appears to be the principal compound in the plant producing psychic effects. However, the influence of many other ingredients of marihuana, such as cannabinol, cannabidiol and the various acid precursor forms of these compounds and THC must be investigated as they may affect the psychoactivity of THC (or hydroxy-THC). There may be other substances which are water soluble, in contrast to the oil soluble cannabinoids, which may also contribute to the overall drug action.

Some of the effects which may be due to chronic heavy marihuana use are changes in personality, motivation, short-term memory and other disturbances of thinking. The possibility that some substances, remaining in the body longer than THC (or even hydroxy-THC), may be causally related to these effects must be entertained. If this is so, these substances should be isolated or made synthetically and their effects and influence on THC action studied.

A major difficulty encountered in the early portion of the metabolism studies was that of measuring THC after it has entered the body. This was found to be due to its rapid transformation into hydroxy-THC and other degredation products. However, as THC is metabolized in this way it

becomes a more polar compound more difficult to separate from other body constituents.

Several ways can be recommended to deal with this. A further development of the very sensitive techniques of radio-immunoassay (immune reactions using radiolabelled compounds) should be capable of achieving the selective and sensitive determination of THC and its metabolites. Other techniques which may be useful are combining gas chromatography with mass spectrometry and the methods of spectrofluorometric analysis.

It is important to develop convenient techniques which quantitatively measure the amount of psychoactive material which is absorbed into the body following marihuana smoking or ingestion. Such measures would be analogous to present blood alcohol tests used to determine levels of alcohol intoxication.

The use of marihuana by man is seldom divorced completely from the use of other drugs. One of the principal difficulties in studying marihuana is that users frequently also use LSD, amphetamines, alcohol, heroin and other drugs. In addition, most people use an extremely long list of common drugs such as aspirin, tranquilizers, caffeine, antihistamines, antihypertensives, antibiotics, etc. The possible interactive effects of these various drugs are not now known and need study.

The interactions between barbiturates and marihuana, especially in the brain and liver, should certainly be studied in order to anticipate problems such as now occur in the simultaneous use of alcohol and

barbiturates. In fact, the admixture of all three - alcohol, barbiturates and marihuana - will predictably occur and must also be studied.

Despite the increase of marihuana research papers since 1968, some actions of marihuana are incompletely understood and their possible significance for health cannot at present be evaluated. These areas can be discussed under the classical organ systems approach commonly used in medicine.

(1) Cardiovascular system. One of the most reliably reproducible indicators of marihuana action is the characteristic acceleration of the heart beat. In addition, large or toxic doses produce a fall in blood pressure. Despite repeated observations of these effects in animals and man, their mechanisms and toxic significance is largely a matter of speculation.

Only a few basic studies on the mechanisms of these actions have emerged but they have not adequately explained them. Studies are needed on isolated and intact hearts and cardiovascular systems as well as a careful checking of the cardiac performance of human marihuana-using subjects. An authoritative evaluation of the risk of this drug for those with heart disease is needed. The risk involved in marihuana use by older people being treated for cardiac conditions with drugs such as digitalis should also be studied.

(2) Liver function. The primary clue linking THC with the liver has been the involvement of this organ in transforming THC into hydroxy-THC and other metabolites. Although marihuana use appears nowhere near

as hepatotoxic as alcohol, the function of this organ should be carefully evaluated by well known clinical tests and in special cases by biopsy. Again, the risk of marihuana in persons with disease-limited liver function should be assessed.

(3) Gastrointestinal function. Since some users take marihuana orally, the gastrointestinal effects of this drug must be evaluated. There is evidence that the drug in large amounts can slow gastrointestinal passage of an experimental meal and relax an isolated intestine although it is not constipating. The sometimes reported enormous increase in appetite following marihuana smoking may also be related to effects in the gastrointestinal tract.

Observations made during metabolism studies have shown a marked persistence in the gastrointestinal tract of certain derivatives of THC, particularly di-hydroxy THC. This appears to be caused by a cyclic process in which the liver secretes metabolic products into the bile and then into the intestine where they remain or may be reabsorbed for recycling. This, and the fact that eating is a primary route of marihuana intake, suggest the need for a careful research consideration of marihuana and gastrointestinal function in the future.

(4) Neuroendocrine effects of marihuana. Little research has been done on the neuroendocrinological effects of chronic marihuana use. Almost all other drugs with strong psychotropic action such as tranquilizers, antidepressants and alcohol can elicit disturbances of those systems controlling stress reactions, gonadal function, growth and the like. Careful studies will be needed in order to evaluate possible

risks to patients with all sorts of mild endocrine disorders of the pituitary, thyroid, adrenal and other glands.

(5) Lung function. Because smoking is the typical mode of use of marihuana in America, studies of its effects on lung function are of considerable potential importance. Carcinogenic liability of marihuana should be investigated using dogs and other animals trained to inhale smoke. Detailed microscopic investigation into the effects of chronic marihuana smoking on the living cells of the tracea and bronchi must be completed, even though preliminary experiments have not shown this form of smoking to be as damaging as tobacco smoking.

(6) Brain function. This is the most important area of future research. It is of critical importance to know the role of chronic marihuana use in some of the behavioral and intellectual changes that have been reported as associated with use. Apart from the implications of chronic, heavy use of such materials as hashish, it is of critical importance to know what, if any, are the implications of use at the much lower levels already occurring or likely to occur for substantial numbers of the population.

Although laboratory research is an important aspect of the study of the relationship of marihuana and health, it must be emphasized that the answers are not ultimately to be found in animal research or in laboratory studies of acute human administration. While such research may provide important clues as to the questions to be posed, the most

important of these can only be answered by careful observation and testing of the many users, here and abroad, who are, in effect, experimenting on themselves. To date long-term chronic studies have not generally been possible with American populations. It will be some time before long-term users exist in adequate numbers to assess the impact of American using habits and exposure to cannabis. Meanwhile continuing efforts are being made to develop a series of overseas studies with a range of human user populations at different levels of use so as to learn the health implications of varying patterns of use. Two such studies are now in progress. In order to control for different variables and to cope with the inevitable deficiencies of any one study, several more will be needed.

In evaluating patterns and histories of use it is important to know more about differences which may be associated with particular ethnic and subcultural aspects.

Little is at present known about the factors that play a role in determining long-term patterns of drug use such as patterns of child rearing, parental attitudes and their personal drug use. How do these affect the use patterns of children? There is evidence that the ways in which parents use tobacco and alcohol are correlated with their children's use. Almost certainly parental attitudes and behavior are related to the use of illicit drugs as well.

To date marihuana use has been largely confined to the youthful portion of the American population - an age group in some respects least likely to show ill effects of a drug. As more representative portions

of the population experiment with the drug, it becomes increasingly important that we know the implications of use for individuals who may be less physiologically or psychologically resilient and who may have a variety of disabilities. This is important not only from the standpoint of chronic use, but also to understand the implications of acute usage for various types of performance and functioning, including such everyday tasks as driving.

Finally, it is of importance to develop effective methods of prevention and education that are likely to deter individuals of all backgrounds and at all levels of risk from adopting pernicious patterns of drug use whether of marihuana or of other drugs abused in our society. To do so we need to better understand the factors in our own and in other cultures which help to socially control drug use and to inhibit drug abuse. Although research in these areas frequently lacks the precision possible in laboratory sciences, it may prove to be in the end the most important in averting drug abuse and its health consequences. Such research should certainly include a better understanding of those aspects of individuals' lives that serve to make drug abuse less attractive and provide tenable alternatives to drug use.

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